ADHERENCE PATTERN, HEALTH CARE UTILIZATION, AND VIROLOGIC OUTCOMES AMONG TREATMENT-NAÏVE VETERAN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 INFECTION

by

Yan Cheng

A dissertation submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in

Pharmacotherapy Outcomes Research and Health Policy

Department of Pharmacotherapy

The University of Utah

August 2017

The University of Utah Graduate School

STATEMENT OF DISSERTATION APPROVAL

The dissertation of **Yan Cheng**

has been approved by the following supervisory committee members:

Joanne LaFleur	, Chair	**04/16/2017** Date Approved
Nancy Nickman	, Member	**04/16/2017** Date Approved
Christine Jamjian	, Member	**04/20/2017** Date Approved
Brian Sauer	, Member	**04/20/2017** Date Approved
Vanessa Stevens	, Member	**04/18/2017** Date Approved
Yue Zhang	, Member	**03/31/2017** Date Approved

and by **Karen Gunning**, Chair/Dean of

the Department/College/School of **Pharmacotherapy**

and by David B. Kieda, Dean of The Graduate School.

ABSTRACT

Many studies have estimated the treatment effect of different antiretroviral therapies (ARTs) on human immunodeficiency virus (HIV) patients' virologic/immunologic outcomes. However, evidence is lacking on how adherence to ARTs influences treatment effects.

The goal of this study is to explore HIV treatment-naïve veterans' health care utilization and to investigate the effect of early adherence on initial viral suppression by different regimens.

A cohort study was conducted on HIV veterans initiating ARTs in 1999-2015. The follow-up time was one year since the first fill of base agent (index date). Patients' health care utilization during the follow-up as well as the correlations between initial adherence and one-year adherence were estimated. The primary outcome was the first viral suppression occurred within thirty to 60 days since the index date. Multiple imputation was used to impute the missing value of virologic outcomes. The inverse probability of treatment weighting (IPTW) method was applied to estimate the viral suppression rate at each specific adherence category for each regimen category. Marginal structural models (MSMs) with IPTW were used to estimate the risk of viral suppression in lower-adherence categories in comparison to near-perfect adherence level ≥95%.

Data showed that all patients had at least one follow-up test or visit in the one year. The mean of initial adherence to the base agent was 0.84–0.90, depending on the regimens,

with unboosted protease inhibitors (PIs) lowest and integrase inhibitors (INSTIs) highest. The correlations between initial adherence and thereafter one-year proportion of days covered (PDC) were medium, estimated at 0.54–0.63. Lower adherence caused lower viral suppression rate, with the association differentiated by the regimen. Patients on INSTIs had the highest viral suppression rate, with patients on PIs having the lowest rate. Regardless of regimens, the viral suppression rate among patients at initial adherence of 75-<95% was not statistically different from patients at adherence of ≥ 95%; however, the differences might be clinically significant.

Initial adherence differently influenced the viral suppression rate across different regimens. Regardless of regimen categories, no evidence shows 95% adherence threshold is necessary.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

There are so many people to thank for their help, support, and encouragement during my past four years. This dissertation would not have been possible without their contributions. I would like to express my sincerely deepest gratitude to them.

First, I would like to thank my advisor and committee chair, Dr. Joanne LaFleur, for her guidance, support, and encouragement throughout the whole duration of my doctoral study and research. It was my great pleasure to work with her on many projects relevant to my dissertation. Without these experiences, I could not have gained the solid research abilities and skills that were critical to the completion of this work. She has been an endless source of knowledge, advice, and inspiration, and has been patient with helping me advance in my graduate career.

I would like to thank Dr. Brian Sauer for mentoring me on the causal inference methods. He provided me with opportunities to deeply learn and understand these methods, as well as to train my critical thinking as a pharmacoepidemiologist. Without his invaluable supports in these methodologies, this project would have been possible.

I would like to thank Dr. Vanessa Stevens for being on my committee and mentoring me on infective disease epidemiology. Especially, I thank for her sharing her doctoral dissertation with me. It was tremendously helpful to me as I prepared my dissertation proposal and documents. Also, her personal suggestions during my pursuit of a PhD have been very constructive and have helped me a lot.

I would like to thank Dr. Yue Zhang for mentoring me on statistical methods. He spent so many hours discussing the methods in my dissertation and answering my statistical questions, such as imputation, censoring, modeling, etc. His insightful suggestions on the statistical methods have made this dissertation feasible and practicable.

I would like to thank Dr. Christian Jamjian for acting as a committee member and contributing her knowledge and expertise in pharmacy and infective disease. I thank her for her time spent going through my data and results and for her suggestions from the standpoints of clinicians and pharmacists.

I would like to express my sincere appreciation to Dr. Nancy Nickman for her contributions of time, helpful suggestions, and expertise in her role as a member of my disseration committee. Especially, I thank her for instructing me on planning dissertation preparation and understanding relevant requirements.

I want to give special thanks to Dr. Marlene Egger for mentoring me on causal inference and advanced statistical methods. Without the many hours that she spent on discussing the complexity of these methods, it would have not been possible to apply these methods to my dissertation.

My research skills and knowledge gained from research projects that I have been involved in have definitely contributed to the completion of this project. My special thanks go to Dr. Diana Brixner, Dr. David Stenehjem, Dr. Joseph Biskupiak, Dr. Brandon Bellows, and Dr. Richard Nelson.

I also have special thanks for Xiangyang Ye. Every time I had questions on statistical techniques or analytical approaches, he was always patient when answering my questions and suggesting the optimal solutions.

Many others, including my fellow doctoral students and research team members, are also deserving of many thanks. In particular, thank Tianze Jiao for numerous methodological discussions; Thomas Reese, and Jacob Crook for their valuable help on data checking and SAS coding; and Ben Yu for his help on programming algorithms.

I would like to address my special thanks to the Veterans Health Administration for their generous provision of the databases for this project.

My thanks extend to all the professors who have taught me professional knowledge and skills through wonderful courses and to all the peer students and colleagues who have helped me in these years.

Special thanks also go to my dear friends from the Salt Lake City Chinese Christian Church. Their encouragement and prayers helped me through difficult times during my PhD.

Last but not least, I would like to express my deepest appreciation to my family. I thank my father, Weidong, and my mother, Xinru, for their endless support with my education. A million thanks go to my dearest husband, Yijun. With his love and support, I have been able to overcome all kinds of difficulties and finally complete this work and finish my PhD.

CHAPTER 1

INTRODUCTION

1.1 Human Immunodeficiency Virus and Immune System Response

The human immunodeficiency virus (HIV) is a virus that can be transmitted via bodily fluids by sexual contact, injection drug use, childbirth, breastfeeding, or blood transfusion.[1] There are two types of HIV infection: HIV-1 and HIV-2. The majority of HIV infections are of HIV-1; HIV-2 is prevalent only in western Africa and in countries related to western Africa.[2] In comparison, HIV-2 has lower transmission risk and is less progressive than HIV-1, due to its persistent lower viral loads.

Once HIV enters the human body, its targets are lymphocytes or T-cells through CD4 molecules and chemokine receptors.[3] The role of T-cells is to facilitate the body's immunity response to cellular abnormalities and infections.[3] If T-cell counts are too low, then the immune system cannot fight infections. [3] At the same time, once HIV contacts a T-cell, it injects its genetic material into the cell. The proteins on the surface of HIV are attached to receptors and co-receptors on the surface of the T-cell, and HIV penetrates the cells and releases its ribonucleic acid (RNA) and enzymes into the cell.[3] Then HIV starts to replicate and damage the immune system by reducing CD4 T-cell count.

Therefore, viral loads and CD4 T-cell counts are the best gauge to evaluate the level of HIV virus and the response of the immune system to the invading virus, respectively. There is an inverse relationship between viral load and CD4 counts. During the early HIV infection, HIV RNA can reach the highest level (>100,000 copies/mL) and CD4 T-cell counts drop sharply before stabilizing at 500-600 cells/mm^3.[4,5] Once the initial infection period has passed, viral loads begin to decrease and remain at a low level due to the immune system response.[6] However, viral loads increase over time, since they destroy CD4 cells, which damages the immune system.[6] There is no normal range for viral loads; clinically, the treatment goal is to suppress viral load to an undetectable level. The optimal viral suppression is generally defined as a viral load persistently lower than 20-75 copies/mL.[5]

For adults or adolescents, the normal range of CD4 counts is 500-1500 cells/mm^3.[7] It is estimated that an untreated HIV patient's CD4 T-cell count drops by about 45 cells/mm^3 every 6 months.[4] When the CD4 cell count drops down to 200-500 cells/mm^3, it indicates some damage has occurred in the immune system; when the CD4 cell count is below 200 cells/mm^3, patients are at high risk of developing an HIV-related illness.[4] It is common to use CD4 counts less than 200 cells/mm^3 to determine if a HIV-positive patient has progressed to acquired immune deficiency syndrome (AIDS).[7] CD4 count is also commonly used to determine when to initiate antiretroviral therapy (ART). The 2013 World Health Organization (WHO) guidelines recommend initiation of ART when a CD4 count drops to $\leq$ 500 cells/mm^3 in all populations, including people in low- and middle-income countries.[8] The recently issued HIV treatment guidelines by the US Department of Health and Human Services (DHHS)

recommend starting ART as soon as possible once the diagnosis of HIV is confirmed.[5] However, the guidelines from European countries suggest initiating ART only among patients with a CD4 count of ≤350 cells/mm^3.[9,10] Although CD4 count is the major factor that is used to decide whether treatment initiation is necessary, some providers may decide to start treatment based on viral loads alone.[6]

1.2 Epidemiology of HIV in the US

It is estimated that more than 1.2 million people in the United States are living with HIV, and about 14% among those are unaware of their infection.[11] About 50,000 and 30,000 people are newly infected with HIV and AIDS, respectively, in the United States annually.[12] The high-risk groups of HIV infections mainly include homosexual and bisexual men and young African-Americans.[11] In 2010, men who have sex with men accounted for 78% of new HIV infection among males and 63% of all new infections; among new HIV infections of men who have sex with men, half of the infections occurred in young African-Americans.[11] African-Americans experience the highest risk of HIV infection of any racial/ethnical groups. It estimated that African-Americans, who represented 12% of the US population in 2010, accounted for 44% of new HIV infections that year.[11] Hispanics and Latinos also have a relatively higher risk of HIV infection than other racial/ethnical groups. In 2010, Hispanics/Latinos represented 16% of the US population but accounted for 21% of new HIV infections.[11]

However, due to early treatment, the life expectancy of HIV patients has improved greatly. On average, life expectancy at age 20 in the US population is approximately 57 years in men and 62 years in women.[13] A systematic review and

meta-analysis study was performed for HIV/AIDS to elicit utilities from patients on a scale ranging from 0 for death to 1 for perfect health. [14] The authors reported that a pooled estimate of utility for AIDS patients, symptomatic HIV patients, and asymptomatic HIV patients was 0.70, 0.82, and 0.94, respectively.[14]

An ongoing research study by the CDC studied the economic burden associated with HIV diagnosis and treatment. They reported that in the health care setting, such as emergency departments, primary care settings, and urgent care centers, the cost per new diagnosis ranged from $1,900 to $10,000 in 2010 dollars; in the nonhealth care setting, such as jails, community-based organizations, and outreach venues, the cost per new diagnosis ranged from $2,946 to $30,392 in 2010 dollars.[15] The study also discovered that the average annual ART treatment cost was estimated to be $23,000 in 2010 dollars per person, and the lifetime HIV treatment costs was estimated to be $379,668 in 2010 dollars.[15]

1.3 Antiretroviral Agents and Treatment Initiation

The primary goals of antiretroviral agents for HIV are to control HIV replication, restore and preserve the immune system, decrease HIV transmission and infections, reduce complications caused by HIV, and improve quality of life and survival.[16] When initiating antiretroviral regimen for treatment-naïve HIV patients, two primary issues need be considered: when to initiate treatment and what regimen to initiate. As for when to initiate, there are multiple factors to consider, involving both disease and patient factors, which include patient's pretreatment viral load, CD4 count, gender, comorbidities, and drug-resistance testing.[5,16] In addition, patients'

readiness for treatment and treatment factors should also be considered, including patient's knowledge of treatment and its benefits and risks, patient preferences and potential adherence, treatment's adverse effects and convenience, and drug-drug interactions.[5,16]

CD4 count is a primary factor to determine when to initiate antiretroviral therapy in many countries. However, the US guidelines recommend to start ART as soon as possible once the diagnosis of HIV is confirmed, regardless of level of CD4 counts.[5]

Currently, there are 6 classes of ARTs available, including nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 antagonists, and integrase strand transfer inhibitors (INSTIs).[5] According to the guidelines, an initial ART regimen generally consists of two NRTIs in combination with an NNRTI, a PI (preferably boosted with ritonavir), an INSTI, or a CCR5 antagonist (namely maraviroc).[5] The regimens for treatment-naïve patients are listed in Table 1.1.[5]

NNRTI-based regimens have virologic potency and durability in treatment-naïve patients, but their major disadvantages include the prevalence of NNRTI-resistant viral strains in ART-naïve patients and the NNRTI's lower barriers for developing drug resistance.[5] PI-based regimens, especially for ritonavir (RTV)-boosted PI-based regimens, also demonstrate virologic potency and durability. Compared to NNRTI-based regimens, patients treated with PI-based regimens develop drug resistance mutations at lower rates, but PI-based regimens are associated with

high pill burden and high potential for interaction with other medications and food.[5] Among all first-line regimens, both NNRTI-based regimens and PI-based regimens are most commonly used among HIV treatment-naïve patients.[5] As for INSTI-based regimens, the primary disadvantages involve a lower genetic barrier to resistance and higher frequency of administration than PI-based regimens.[5] As for CCR5 antagonists-based regimen, patients are more likely to discontinue therapy due to lack of efficacy than those treated with PI- or NNRTI-based regimens.[5] In the recent two decades, fixed-dose combinations of ARTs were developed and approved to help reduce pill burden.

1.4 Adherence to Antiretroviral Agents

The guidelines recommend physicians delay initiating ARTs among patients who would potentially have poor adherence, because suboptimal adherence is associated with many problems, such as virologic failure, drug-resistance, lowered immunity, and increased morbidity and mortality.[5] However, there is controversy on whether near-perfect adherence (adherence ratio ≥95%) is necessary. Many studies found that the response of the HIV virus to ARTs appeared to be linear rather than having a threshold.[17-34] Some studies found patients at medium adherence level could still achieve viral suppression without developing drug resistance.[35,36]

However, these studies have limitations. They evaluated association between adherence and outcomes, not the causal effect of adherence on outcome. They also simply used a cumulative measure for adherence and an end point measure for viral load and CD4 T-cell count without addressing time-dependent confounder bias. Besides, no study

investigated the effect of early adherence on initial viral suppression, and it remains unclear on the association between early adherence and long-term adherent behavioral. Furthermore, adherence to INSTI-based regimens were rarely studied in the published studies. To fill the existing research gap, the goal of this study was to explore HIV treatment-naïve veterans' adherence, visits and monitoring patterns, and also to investigate the effect of early adherence to ARTs on initial viral suppression by different regimens.

Table 1.1 Recommended and Alternative Antiretroviral Regimen Options for Treatment-Naive Patients[1, 2]

Recommended Initial ART Regimen Options for All Patients, Regardless of PreART Viral Load or CD4 Cell Count
NNRTI-Based Regimen: • EFV/TDF/FTC[3] PI-Based Regimens: • ATV/r plus TDF/FTC[3] • DRV/r plus TDF/FTC[3] INSTI-Based Regimens: • DTG plus ABC/3TC[3]—only for patients who are HLA-B*5701 negative • DTG plus TDF/FTC[3] • EVG/cobi/TDF/FTC—only for patients with pretreatment estimated CrCl ≥ 70 mL/min (AI) • RAL plus TDF/FTC[3]
Additional regimens recommended for patients with preART plasma HIV RNA <100,000 copies/mL
NNRTI-Based Regimens: • EFV plus ABC/3TC[3]—only for patients who are HLA-B*5701 negative • RPV/TDF/FTC[3]—only for patients with CD4 cell count >200 cells/mm3 PI-Based Regimen: • ATV/r plus ABC/3TC[3] – only for patients who are HLA-B*5701 negative
Alternative Initial ART Regimen Options[4]
PI-Based Regimens: • DRV/r plus ABC/3TC[3]—only for patients who are HLA-B*5701 negative • LPV/r (once[5] or twice daily) plus ABC/3TC[3]—only for patients who are HLA-B*5701 negative • LPV/r (once[5] or twice daily) plus TDF/FTC[3] INSTI-Based Regimen: • RAL plus ABC/3TC[3]—only for patients who are HLA-B*5701 negative

[1] This table has been updated; please check current guidelines.

[2] Key to acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = ritonavir-boosted atazanavir; cobi = cobicistat; CrCl = creatinine clearance; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = ritonavir-boosted lopinavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

[3] 3TC may be substituted for FTC or vice versa. The following combinations in the recommended list above are available as co-formulated fixed-dose combinations: ABC/3TC, EFV/TDF/FTC, EVG/cobi/TDF/FTC, LPV/r, RPV/TDF/FTC, and TDF/FTC.

[4] Regimens that are effective and tolerable, but that have potential disadvantages when compared with the recommended regimens listed above or have less data from randomized clinical trials. An alternative regimen may be the preferred regimen for some patients.

[5] Once daily LPV/r is not recommended for pregnant patients.

CHAPTER 2

LITERATURE REVIEW

Published literature indicates that there is an association between adherence to ARTs and patients' viologic/immunologic outcomes, but little is known about whether near-perfect adherence is necessary for patients to achieve optimal virologic/immuniologic outcome or if the association differs for different regimens. Therefore, this literature review was to summarize what has been found in previous studies and to identify the research gap that exists.

2.1 Association between Adherence to ARTs and Virologic/Immunologic Outcomes

A systematic review of the published literature evaluated the adherence "threshold" assumption. The 95% threshold assumption originated with an observational study of unboosted PI by Paterson et al., [30] which reported, in a small cohort of 81 US veterans, that among the unreported and presumably very small number of patients with at least 95% adherence, a much lower percentage of them experienced virologic failure (22% vs. 55–82%, $p<0.001$). However, this finding was descriptive in nature and was unadjusted for observation time, baseline viral load and CD4 cell count, race/ethnicity, comorbid depression, and the particular PI used in the regimen. In fact, in the inferential analysis that

followed the descriptive findings in their paper, investigators did adjust for each of those variables. They conducted a multivariable Cox Proportional Hazards regression model, which adjusts for differences in follow-up time, and used adherence as a continuous measure, implying that they considered the relationship between adherence and outcomes to be linear on the log-hazard scale and not a threshold effect. They reported that, for each 1% absolute increase in adherence percentage, the risk of virologic failure decreased by a relative 3%. Thus, the 95% threshold seems to have been a misappropriated, preliminary finding that was subsequently applied as evidence supporting the 95% adherence doctrine in later HIV health care practice.

2.1.1 Literature Review Procedures

A systematic review to evaluate the association between adherence to ARTs and virologic/immunologic outcomes was conducted in 2015. The goal was to identify and characterize evidence supporting or refuting the claim that highly active antiretroviral therapy (HAART)'s efficacy on virologic and immunologic outcomes occurs at a 95% adherence threshold. The systematic literature review focused on English-language observational studies on HAART adherence that were published in January 2000 through 2015. PubMed was searched using the search string "Antiretroviral Therapy, Highly Active"[Mesh] AND ("HIV"[Mesh] OR "Acquired Immunodeficiency Syndrome"[Mesh]) AND ("Patient Compliance"[Mesh] OR "Medication Adherence"[Mesh]) AND ("humans"[Mesh] AND English[lang]) and eliminated all articles without abstracts. Five inclusion criteria were involved in this search: 1. Is it an observational study that evaluates patient adherence to ARTs? 2. Did

the study include adults (18+ years of age)? 3. Did the article report the methods used to evaluate HIV antiretroviral adherence? 4. Did the article report descriptive statistics for that adherence? 5. Did the study report on an evaluation of the association between patient antiretroviral adherence and either virologic or immunologic outcomes?

2.1.2 Literature Review Findings

A total of 419 citations were identified with the initial PubMed search. After abstract, date range, and eligibility criteria were applied, 139 studies (33.2%) were deemed to address adherence in the required amount of detail. Of these, 56 (13.4%) evaluated the association between patient adherence to ARTs and outcomes of interest. During full text review, 4 additional articles that satisfied all eligibility criteria were identified from the references.

The sample sizes of the studied populations ranged from 35 to 6,395 patients: 10 studies had sample sizes less than 100,[17,18,24,30,37-42] 24 had sample sizes of 100 to 299,[19,20,22,23,33-35,43-59] 7 had sample sizes of 300 to 499,[28,36,60-64] 10 had sample sizes of 500 to 999,[25,27,29,31,65-70] and 8 had sample sizes of more than 1,000.[21,26,32,71-75] Only 4 studies included veterans as the target study population,[21,22,30,31] and 3 studies included women only.[19,46,57] In terms of source populations, 20 studies were evaluations of United States (US) patients samples, [17-24,30,31,34-36,40-44,57,58] 20 were European, [26,27,37-39,46,51,53-56,59,60,62,63,66,68,69,71,76] 8 were Canadian, [25,32,50,61,67,72,74,75] 7 were African, [28,29,33,45,47,52,73] 4 were Asian, [48,49,64,70] and 1 was Australian. [65]

In terms of study designs, cohort studies were the most prevalent, with 47 in all, including 16 historical cohort studies [19,21,22,25,32,36,39,45,46,48,54,69,72-75] and 31 prospective

cohort studies. [17,18,20,23,26,27,29,30,34,35,37,40,41,43,44,50,51,53,55-58,60,61,65-68,70,71,76] There were also 10 cross-sectional studies, [24,31,33,42,47,49,59,62-64] and 3 case-control studies.[28,38,52] Among the cohort studies, 7 studies had a long-term follow-up of at least two years,[25,60,65,70,73,75,76] and 4 studies had varied follow-up time with the median duration longer than two years,[32,48,50,72] 13 had a follow-up duration of at least one year, [20,34-36,43-46,51,55,56,61,74] and 1 study had varied follow-up time with the median duration longer than one year,[69] 17 had a follow-up duration of at least six months, [17-19,21,23,27,29,37,39-41,53,54,57,58,67,71] and 4 had a short-term follow-up less than six months.[22,26,30,68]

In terms of the ART regimens evaluated, most studies explored the effects of adherence to any antiretroviral agents; however, a total of 12, 9, and 4 studies investigated both PI- and NNRTI-based regimens, [20,22,25,26,32,34,43,45,67,72,74,75] only PI-based regimens, [30,37,40,41,51,55,60,61,68] and only NNRTI-based regimens, [38,47,48,73] respectively. In addition, 1 study [56] included both NNRTI-based regimens and triple NRTI regimens as the treatments of interest.

A summary of important findings from the studies is given in Table 2.1. Among studies that analyzed adherence measured as continuous variables, 20 reported using linear assumptions in their evaluations of the relationship between adherence and outcomes. Of these, 18 [17-34] showed statistically significant results and 2 [40,66] did not. Among 48 studies that analyzed adherence as a categorical variable, 18[17,20,21,25-27,29,35-38,40,41,43,44,60,65,72] reported a statistically significant effect at some threshold, 4 [23,32,55,73] reported an evenly distributed dose-response relationship between adherence and outcomes (in other words, a dose-response relationship without an obvious threshold), and 5 [52,53,56,57,69] reported that adherence had no effect on outcomes. However, of the 48 studies that analyzed adherence

as a categorical variable, 20 [22,24,33,42,45-48,50,51,54,58,59,61,63,64,66-68,74,75] only included dichotomized adherence in the analysis, masking any information about whether there was a threshold or linear effect.

In the studies that evaluated multilevel categorical adherence to PIs, 2 [26,55] reported evenly-distributed dose-response relationships for PI-based regimens and 7 [20,27,37,40,41,43,60] identified a threshold effect at levels ranging from 65.6% to 86%, lower than the 95% threshold that is commonly accepted in HIV care practice. For NNRTI-based regimens, 1 study [73] reported evenly-distributed dose-response effects of adherence on outcomes over follow-up durations of three to nine months but showed a threshold effect at 80% adherence when follow-up was longer than nine months; 5 other studies [17,26,27,38,43] identified the different adherence thresholds, ranging from 49% to 86%, which were lower than the PI threshold. Another 2 studies reported an evenly-distributed dose-response association between adherence and virologic outcomes[32] and between adherence and combined virologic/immuniologic outcomes[25], respectively, while 8 [17,21,23,29,35,36,44,65,72] identified a threshold effect with the range of 40%-97%; one [65] of these was at 95% and 3 [17,36,44] were at 90% adherence thresholds. A single study reported a threshold effect of adherence on immunologic outcome at an adherence level of 95%.[23]

We found that there was very little in the literature to support the "threshold" assumption at 95%. While at an individual level, virologic failure is a dichotomous outcome that occurs at many adherence levels lower than 95%, at the population level, virologic suppression appears to go up in direct, continuous relationship to adherence. Nonetheless, a few studies supported a threshold effect, but most at levels lower than 95%. It was apparent that the threshold seemed to vary depending on the regimen, with NNRTI-

based regimens requiring lower levels of adherence compared to PI-based regimens across the board.

The systematic review also suggested that a lower adherence level would be unproblematic with newer drugs, since NNRTIs require lower adherence rate than PIs. Another systematic review by Kobin and Sheth has confirmed that newer class ARTs need only lower adherence levels to achieve and maintain suppression. [77] They discovered that the appearance of potent ARTs (i.e., boosted PIs and NNRTIs) has dropped the required amount of adherence since 1990s.

Based on existing literature, the response of the HIV virus to current HAART regimens appears to be linear rather than having a threshold, as has been commonly promoted. Furthermore, most HIV-infected patients never approach guideline-recommended adherence to HAART.

2.2 Limitations of Adherence Studies

The majority of studies evaluated the association between long-term adherence and outcome; however, most of them did not measure adherence, viral load, or CD4 T-cell counts as time-dependent variables. Rather, they used a cumulative measure for adherence and an end point measure for viral load and CD4 T-cell counts. Without handling time-dependent confounders, the estimates of the relationship may be biased. Although 1 study handled time-dependent confounders, this study did not measure adherence to different regimens separately.[35]

Since there is complexity to estimate the unbiased long-term adherence effect on disease outcomes, there are not sufficient studies to estimate the initial adherence effect

and how the initial adherence is correlated to the adherence in the long term. Such studies are very important and supportive to further understand adherence pattern and the mechanism of how adherence influences disease outcomes when time matters.

Furthermore, INSTI-based regimens, which are preferred to treat HIV treatment-naïve patients, and recommended by current guidelines, have been rarely studied in the published literature to evaluate the association between adherence and outcome. Since guidelines recommend physicians consider patients' compliance when deciding whether or not to start HIV treatments and suggest the delay of antiretroviral therapy for those who are nonadherent, it is important to understand how adherence to ARTs influences patient outcomes differently when class of regimen is also taken into account.

Table 2.1 Summary of Findings from Systematic Review

Reference	Key information
Arnsten et al., 2001, Clin Infect Dis (PMID 11550118)[17]	Key information: • Correlation coefficients imply a linear relationship. • One-day adherence may overestimate adherence because of increased medication-taking on the day preceding a clinic or research visit • There appears to be high correlation between self-report and MEMS adherence. • Self-report adherence seems to exaggerate real adherence levels. Patients were more likely to self-report a high (>90%) or medium (50–89%) adherence level than MEMS adherence measures; however, patients with a high or medium self-reported adherence level had lower incidence rate of viral suppression than those with the same MEMS adherence level.
Arnsten et al., 2002, J Gen Intern Med (PMID 12047736)[18]	Key information: • Analytic approach implies a linear relationship between adherence and outcomes. • 15% of subjects were antiretroviral naïve.
Aziz et al., 2013, BJOG (PMID 23924192)[19]	Key information: • Adherence was used as a continuous variable in the multivariable analyses. • Improved adherence was statistically significantly associated with viral load <400 or <1000 copies/ml. • The study population was pregnant women.
Bangsberg et al., 2003, AIDS (PMID 12960825)[44]	Key information: • Patients with adherence level of 0–41%, 42–57%, 58–78%, 79–91%, and 92–100% had a proportion of 10%, 26%, 34%, 32%, and 57% patients achieved viral suppression. • It seems that 92% had a threshold effect there. There was no difference in adherence of 58–78% and 79–91% on viral suppression.
Bangsberg et al., 2006, Clin Infect Dis (PMID 16941380)[43]	Key information: • The 95% threshold was only true for PI-based regimens, not for NNRTI-based regimens, and the magnitude of difference between 74–94% and 95–100% was not that substantial. • The link between adherence and outcome was based on the PI or NNRTI adherence, not the whole regimen.
Bangsberg et al., 2006, AIDS (PMID 16511415)[20]	Key information: • Correlation statistics imply a linear relationship. • PIs looked dramatically superior for patients with high adherence (≥77%) but worse for patients with low adherence (<77%). • For patients treated with NNRTIs, decreased adherence seemed to be associated with slightly reduced viral suppression rate if adherence rate was ≥49%. But once adherence rate was <49%, the viral suppression rate dropped very quickly. • Multivariable models may have been overfitted, since only 54 patients were on each regimen type.

Table 2.1 Continued

Reference	Key information
Bastard et al., 2011, J Acquir Immune Defic Syndr (PMID 21775934)[45]	Key information: • 95% was used as a threshold to dichotomized adherence; continuous adherence was not used in the study. • The study did not separate the adherence to PIs and to NNRTIs.
Braithwaite et al., 2007, AIDS (PMID 17630553)[21]	Key information: • Used the 500 copies/mL threshold to define "suppression". • Increased adherence and decline in HIV-RNA appeared to be linearly associated. However, there was little difference for single PI, because for patients with an adherence level within 80–100%, patients who had a higher adherence did not increase decline in HIV-RNA. • For all regimen categories, when viral suppression was used as an outcome, it seemed that for patients with an adherence level within 80–100%, patients who had a higher adherence did not have an increased rate of viral suppression.
Carrieri et al., 2003, Antiviral Therapy (PMID 14760892)[60]	Key information: • The study measured time-dependent adherence, VL, and CD4. • For initial adherence, highly adherent was statistically associated with virologic suppression and increase of CD4count. This might suggest a threshold effect of adherence on virologic and immunologic outcomes. • For M12–M36 adherence, moderate and high adherence had similar effect on viral suppression, but both were statistically different from nonadherence. However M12–M36 adherence cannot predict immunologic outcome at all. • There was a threshold effect at adherence 80% when follow up time was longer than 12 months. The suppression rate among 100%, 80–99%, and <80% adherent patient were 64.5–71.3%, 61–66.4%, and 30.4–53.8%.
Combescure et al., 2009, HIV Medicine (PMID 19459990)[71]	Key information: • The study explored the probability that the n+1 viral load would exceed 50 or 1000 copies/mL when the n previous viral load was <50 copies/mL. • After several successive viral loads at < 50 copies/mL, reliability reaches approximately 94% with a cutoff of 50 copies/mL, and approximately 99% with a cutoff at 1000 copies/mL. • The reliability increased if adherence was improved.
Dragović et al., 2014, Women Health (PMID 24555810)[46]	Key information: • Self-reported adherence was used. Good adherence was measured as adherence>90%. • Adherence of >90% was independently associated with favorable virologic and immunionlogic outcome.

Table 2.1 Continued

Reference	Key information
Fairley et al., 2005, HIV Medicine (PMID 16156886)[65]	Key information: • Adherence based on pharmacy record had a threshold effect on virological outcome (viral load < 400 copies/mL). When adherence was less than 80%, then the percentage of patients with viral load <400 copies/mL fell below 35%; when adherence was higher than 80%, then the percentage was in the range of 53–66%. The similar observation was not found for patient-reported adherence.
Ford et al., 2010, PLoS One (PMID 20485480)[47]	Key information: • 95% was used as a threshold. Adherence was independently associated with viral failure.
Ghate et al., 2013, Indian J Med Res (PMID 23760381)[48]	Key information: • Descriptive analysis was for the association between adherence and outcome. • Adherence >95% was necessary for patients to achieve favorable outcome.
Gross et al., 2006, J Infect Dis (PMID 16991085)[32]	Key information: • The study did not identify a clear threshold effect for adherence. • Patients with greater adherence had a greater likelihood of maintained suppression even below the 95% threshold. Incremental increases in adherence at levels <95% should be viewed as a worthwhile goal.
Grossberg et al., 2004, Journal of Clinical Epidemiology (PMID 15528063)[22]	Key information: • Refill-defined adherence performed better than the self-reported adherence to predict viral load change. • Pharmacy-based refill adherence had linear relationship with viral load. Self-report adherence might have threshold association (85% as a cutoff).
Haubrich et al., 1999, AIDS (PMID 10397541)[23]	Key information: • Most patients in the study would fell in the lowest adherence category. • For CD4 cell counts, the threshold for diminishing returns was adherence=100%; adherence levels >90% were associated with reduced efficacy, although there was no significance test of this question. • Investigators reported a statistically significant "linear trend" for the relationship between adherence and both virologic and immunologic outcomes. • The study did not adjust for confounding.
Hong et al., 2013, PLoS One (PMID 23509605)[33]	Key information: • Bivariate analyses were conducted between adherence and virologic suppression. • Only MPR was found associated with outcome. • The threshold of <75% MPR was significantly associated with virologic failure ≥5000 copies/ mL at 6 months. This finding suggests that MPR may be a useful tool to help identify patients at risk for early virologic failure in Namibia and similar settings.

Table 2.1 Continued

Reference	Key information
Huong et al., 2011, Int J STD AIDS (PMID 22096052)[49]	Key information: • They investigated several measures of self-reported adherence, but none of them were associated with risk of virological failure.
Julian et al., 2010, Ann Pharmacother (PMID 20442352)[24]	Key information: • Regardless of using continuous SPNS score or score categories, SPNS was statistically significantly associated with viral load.
Kerr et al., 2012, Drug Alcohol Depend (PMID 22245312)[50]	Key information: • Threshold effect (≥95%) of adherence on HIV RNA viral suppression among injectable drug user.
Knobel et al., 2009; HIV Medicine (PMID 19490179)[66]	Key information: • The study used 90% as a cutoff of adherence. The outcome was treatment failure including death and viral load >500 copies/mL. • For patients with follow-up time longer than 3 years, continuous adherence did not reach statistical significance.
Kuyper et al., 2004, J Acquir Immune Defic Syndr (PMID 15602125)[67]	Key information: • The study did not use adherence as a continuous variable. Patients with adherence <95% experienced more rapid viral rebound rates.
Le Moing et al., 2001, J Acquir Immune Defic Syndr (PMID 11468425)[68]	Key information: • Self-reported adherence was measured and taking 100% of scheduled pills was reported as full adherence. • Adherence was only statistically related to early virologic response at M4 but not to early immunologic response at M4.
Lima et al., 2008, AIDS (PMID 18981777)[25]	Key information: • Regardless of the regimen received, it seemed that there was a linear relationship between adherence immunologic/ virologic responses. • 95% adherence might only be required for unboosted PI regimen. • In patients treated with NNRTI-based regimens, adherence level of 80%–<95% their outcomes were still good.
Lima et al., 2010, J Acquir Immune Defic Syndr (PMID 20838225)[72]	Key information: • There was no obvious dose-response relationship between adherence and risk of viral rebound, after adjusting for duration of suppression. • Adherence level of 40% to < 80% was not worse than adherence level of 80% to <95% according to its effect on virologic rebound.
Liu et al., 2006, J Acquir Immune Defic Syndr (PMID 16540932)[34]	Key information: • With the increased follow-up duration, the effect size of adherence on the change of viral load would also increase. • With the increased follow-up duration, the effect size of dose-timing error on the change of viral load would also increase.

Table 2.1 Continued

Reference	Key information
Lopez et al., 2006, HIV Clin Trials (PMID 17065027)[69]	Key information: • In multivariate Cox model, adherence itself was not statistically associated virologic failure, but the interaction term of ddI-EC with food according to adherence level was statistical significant. In this study, adherence at 80% was identified as a cutoff.
Maggiolo et al., 2005, Clin Infect Di (PMID 15614706)[27]	Key information: • For NNRTI-based regimen, there was a linear relationship between adherence and outcome. • However, for PI-based regimen, there might be a threshold effect at adherence level of 85%.
Maggiolo et al., 2007, HIV Clin Trials (PMID 17956829)[26]	Key information: • There was linear relationship between adherence and viral rebound. • However, for single and boosted PI based regimens, 95% threshold might be important.
Marconi et al., 2013, AIDS Patient Care STDS (PMID 24320011)[28]	Key information: • Pill count adherence has linear relationship with the risk of virologic failure.
Messou et al., 2011, J Acquir Immune Defic Syndr (PMID 21191309)[29]	Key information: • There was a linear relationship between adherence and viral load suppression. • Compared to adherence of >95%, adherence level of 80–95% was only significantly associated with higher chance of virologic failure and wild type HIV-1 but not virologic failure and resistance. This indicated that 80% might be an important threshold of adherence to predict combined outcome of viral load and resistance.
Moore et al., 2006, HIV Med (PMID 16945076)[61]	Key information: • In the study, the researchers did not include continuous adherence as a variable, instead they used 90% as a cutoff to dichotomize adherence. • The article studied PI-based regimens.
Moreno et al., 2000, Antivir Ther (PMID 11142618)[51]	Key information: • In the study, the researchers did not include continuous adherence as a variable, instead they used 90% as a cutoff to dichotomize adherence. • The article studied PI-based regimens.
Murri et al., 2009, AIDS Patient Care STDS (PMID 19183079)[62]	Key information: • This is a study about self-reported adherence, but no percentage adherence was used. • The results based on univatiate analyses.
Nachega et al., 2007, Ann Intern Med (PMID 17438315)[73]	Key information: • The study was based on NNRTI-based regimens. • The dose response relationship between adherence and both viral suppression and subsequent viral failure was observed.

Table 2.1 Continued

Reference	Key information
Ncaca et al., 2011, PLoS One (PMID 21858001)[52]	Key information: • In the study, treatment interruption might be more important than cumulative adherence to predict viral failure. Neither adherence <90% nor <95% was associated with increased risk of viral failure compared to adherence ≥90% and ≥95%, respectively.
Nellen et al., 2009, AIDS Care (PMID 20024740)[53]	Key information: • In the study, 85% was used a cutoff to dichotomize adherence. However, the lower adherence level did not predict viral failure well. It might because that sample size was too low to have statistical significant results. • Only "reporting to stop medication when not feeling well" had a statistically significant odds ratio of virologic failure. • The study did not adjust covariates.
Nieuwkerk et al., 2010, Antivir Ther (PMID 20834104)[63]	Key information: • Percentage adherence was not measured. • Instead, four questions were used to measure adherence. Median level of adherence was selected as a cutoff. Adherence was only associated with viral suppression for patients with lower social desirability.
Parienti et al., 2008, PLoS One (PMID 18665246)[38]	Key information: • All treatments were NNRTI-based. Patients with ≥80% average adherence all achieved virologic control.
Parienti et al., 2013, Antimicrob Agents Chemother (PMID 23459496)[37]	Key information: • The study measured time-dependent adherence and outcome. The studied regimens were boosted PI-based regimens. • In longitudinal analyses, adherence measures were significantly associated with DVS; however, adherence was not related to virologic outcomes in cross-sectional analyses. • Timing compliance performed better than other MEMS measures to predict DVS. The cutoff to maximize the accuracy of prediction was 78%.
Parruti et al., 2006, AIDS Patient Care STDS (PMID 16426156)[54]	Key information: • The cutoff of adherence was 90%. The researchers did not use continuous adherence as an outcomes. • The follow-up time was at least 24 months, which indicates that interventions to improve adherence should be prolonged for at least 24 months.
Pasternak et al., 2012, J Infect Dis (PMID 22927449)[39]	Key information: • Compared to the optimal-adherence group, the poor-adherence group significantly higher viral load. • However, the improving-adherence group did not have the significantly increased mean of viral load.

Table 2.1 Continued

Reference	Key information
Paterson et al., 2000, Ann Intern Med (PMID 10877736)[30]	Key information: • Each 1-unit increase in adherence was associated with a 3% decreased risk of virologic failure, which indicated the linear relationship between adherence and outcomes. • Doses taken early were not considered "dosing errors". • The study population was mixed incident and prevalent users.
Perez-Elias et al., 2003, HIV Clin Trials (PMID 14628282)[55]	Key information: • Multivariate analyses indicated that > 90% adherence was statistically associated with viral suppression. • The study was based on PI-based treatment, and it indicated that 95% might not be necessary. • Dose response relationship was observed. Compared to indinair, nelfinavir performed better when adherence was controlled.
Perez-Elias et al., 2005, HIV Clin Trials (PMID 16452065)[56]	Key information: • Adherence was not related to the viral suppression in the multivariate analysis.
Pujades-Rodriguez et al., 2011, Trop Med Int Health (PMID 21087376)[64]	Key information: • The relationship between adherence and viral failure was based on a univariate analysis. • Self-report adherence was measured using 100% as a cutoff.
Rosenblum et al., 2009, PLoS One (PMID 19787058)[35]	Key information: • Adherence was measured as a time-dependent variable. Marginal structural model was applied in this study. • The risk of virologic failure for adherence greater than 50% declines with longer duration of continuous suppression. It may suggest that once patients achieve viral suppression, suboptimal adherence level ≥50% is also acceptable.
Sethi et al., 2003, Clin Infect Dis (PMID 14523777)[36]	Key information: • No response trend was observed between adherence and viral rebound. • Compared to patients with adherence of 100%, only patients with adherence of 70–89% had a significant quicker time to have viral rebound.
Sha et al., 2011, HIV Clin Trials (PMID 21388937)[57]	Key information: • Adherence was not related to viral rebound in this study.

Table 2.1 Continued

Reference	Key information
Shuter et al., 2007, J Acquir Immune Defic Syndr (PMID 17460469)[40]	Key information: • Neither self-reported adherence nor MEMS adherence was associated with viral suppression. • The study was based on univariate analyses. • Self-reported adherence rate of >77.5–92.9% had the highest percentage of viral suppression.
Shuter et al., 2009, HIV Clin Trials (PMID 19632952)[41]	Key information: • The study is for evaluating the relationship between adherence to boosted PI-based regimen and viral suppression. • The study was based on univariate analyses. • Adherence of 65.6–85.5% and 85.1–98.7% had almost the same percentage of viral suppression. It seems that the effect threshold of adherence on viral suppression was at 65.5% in this study.
Singh et al., 1999, Clin Infect Dis (PMID 10589897)[58]	Key information: • Adherence was dichotomized using 90% as a threshold. • The association was based on univariate analyses which did not adjust for confounding.
Sledjeski et al., 2005, AIDS Patient Care STDS (PMID 16283833)[42]	Key information: • 100% was used as a cutoff. Adherence had significantly higher CD4 cell counts in the past 2 days, past week, and past 2 weeks.
Sumari-de Boer et al., 2012, AIDS Behav (PMID 22198315)[59]	Key information: • In the study 100% self-reported adherence and 100% pharmacy fill adherence were used a cutoff. • Nonadherence significantly predicts viral load>40 copies/mL in both 1 month and 6 month time frames.
Vallabhanei et al., 2012, AIDS Care (PMID 22107044)[70]	Key information: • Treatment interruption was significantly associated with higher risk of virologic failure. • The finding was based on univariate analysis.
VanVaerenbergh et al., 2002, Antivir Chem Chemother (PMID 12495211)[76]	Key information: • Only drug taking adherence and the number of drug holidays reached a statistically significant difference. • The results were based on univariate analyses.
Wagner et al., 2001, J Clin Epidemiol (PMID 11750214)[31]	Key information: • Both patient- and provider- reported adherence predicted continuous viral loads. However, only provider-reported adherence was related to viral suppression.

Table 2.1 Continued

Reference	Key information
Wood et al., 2003, CMAJ (PMID 14517122)[74]	Key information: • 95% was used as a threshold for adherence. Adherence was always significantly associated with viral suppression and viral rebound.
Wood et al., 2004, J Acquir Immune Defic Syndr (PMID 15076240)[75]	Key information: • For patients with baseline CD4 count<200 cells/mm^3, there was dose-response between adherence and immunologic response; for patients with CD4 count≥200 cells/mm3, there was a threshold effect between adherence and outcome at adherence level of 75%.

CHAPTER 3

OBJECTIVES, AIMS, AND SIGNIFICANCE

3.1 Objectives

Compliance with medical recommendations and drug therapy is thought to improve viral suppression and quality of life while reducing drug resistance and mortality risk through observational registry data. It remains unknown whether these findings can be reproduced in HIV patients' receiving normal care through the Veterans Health Administration (VHA) system in the United States. Many studies focus on the effect of initiating HIV therapy and ignore the impact of adherence to treatment. The goal of this study was to explore HIV treatment-naïve veterans' adherence, visits and monitoring patterns, and also to investigate the effect of early adherence to ARTs on initial viral suppression by different regimens.

3.2 Specific Aims

The purpose of Aim 1 was to understand ARTs use patterns in a VHA cohort of newly initiated HIV patients. Specifically, the study aimed to: 1) describe patient characteristics for the study cohort and patient characteristics for subgroups on different initiated regimens; 2) identify initial refill patterns and initial adherence to base agent and complete regimen measured by the coverage ratio; and 3) estimate one-year adherence to

ARTs starting from the second fill of base agent, which will be measured as proportion of days covered (PDC) for base agent and complete regimen.

Aim 2's purpose was to assess patients' HIV health care utilization during one year since the first fill date of base agent. Specifically, the frequency of visits for HIV care and lab testing for HIV treatment for the whole cohort and for the subgroups stratified by different characteristics were described.

Aim 3's purpose was to evaluate the correlation between the coverage ratio for the first fill and one-year adherence after initial fill for both base agent and complete regimen.

Finally, Aim 4's purpose was to differentiate patient characteristics at different adherence levels and to estimate the unbiased effect of the coverage ratio for the first fill of complete regimen on virologic outcome that occurred within thirty to 60 days after initial fill date of base agent.

3.3 Study Significance

This study not only aimed to address limitations of previous published studies, but also had many clinical and scientific significances, as described below.

3.3.1 Clinical Significance

In the published literature, there was a lack of studies to describe physicians' prescribing habits, for example, who were more likely to prescribed NNRTI vs. boosted PI regimens. For the initial regimen, many questions remained, such as what patient adherence to the first fill would be and if patients who started with some regimens would have higher adherence than those who started with other regimens. This study aimed to answer these

questions.

3.3.2 Scientific Significance

It remained unknown how HIV patients receive normal care through the VHA system. Aim 2 explored this issue. Missing values or censoring issues was another critical problem in the observational study but was often neglected by researchers. If missing values could not be handled appropriately (i.e., just simply excluding them from the study), then it would incur selection bias. In this study, patients who had missing data of virologic outcomes were distinguished from patients who were less likely to be lost to follow-up.

Previous study discovered that patient baseline characteristics alone could not predict a veteran's adherence to ARTs.[78] The current study evaluated the correlation between initial adherence and one-year adherence to see if the long-term adherence would be predictable according to the initial adherence.

Many published studies made contributions to understanding the association between adherence and health outcomes, but rare studies evaluated the causal effect of adherence to ARTs on virologic outcome. Without taking patients' probability of different adherence levels into account and handling selection biases, the estimates of the effect of adherence on outcome might be biased. Published studies also rarely compared the effect of adherence on virologic outcome across different regimens. For example, INSTI-based regimens, the preferred regimens to treat HIV treatment-naïve patients and recommended by current guidelines, were rarely studied in the published literature. All these questions will be addressed in this study. MSMs were applied by adjusting inverse probability treatment weighting (IPTW) and addressing missing data issues to handle both

confounding bias and selection bias to result in an unbiased causal effect estimate. This approach has evidenced that IPTW can create a pseudo-population where exposure and confounders are uncorrelated, so that it can handle confounding bias appropriately. [79]

CHAPTER 4

METHODS

4.1 Study Design

4.1.1 Study Time Frame

This was a nationwide, historical cohort study on antiretroviral-naïve patients with incident HIV infection initiating ARTs in the VHA system between January 1, 1999, and December 31, 2015. The follow-up time was one year from the first fill of base agent; specifically, for estimating the effect of initial adherence to ARTs on virologic outcomes, the follow-up time was 60 days since the first fill of base agent. The first fill date of base agent was defined as index date in this study.

4.1.2 Data Source

The data source for this study was from VHA databases, which contain data on utilization (pharmacy records, inpatient and outpatient encounters); clinical parameters (vital signs, laboratory results, radiology reports, etc.); and patient eligibility/demographics (age, sex, race/ethnicity). The analytic dataset will be created from the Medical SAS (MedSAS), Decision Support System (DSS), and Corporate Data Warehouse (CDW) datasets. The MedSAS datasets provide national administrative data for inpatient and outpatient health care received by veterans. The

MedSAS datasets contain procedure and diagnosis codes as well as inpatient and outpatient pharmacy data. The DSS datasets are comprised of longitudinal inpatient and outpatient clinical data. The DSS datasets contain laboratory data, including HIV viral load and CD4 cell counts, as well as pharmacy prescription data. The CDW datasets contain both clinical and administrative data. The CDW contains information about inpatient and outpatient visits including procedure and diagnosis codes, vital signs, and outpatient pharmacy data.

4.1.3 Study Population

The study cohort was defined as the VA patients with HIV-1 or AIDS identified by using the International Classification of Diseases Version 9th (ICD-9) codes of 042 or V08 from national VHA databases. Patients were included if satisfying the following inclusion/exclusion criterion: 1) having at least one ICD-9 code of HIV-1 or AIDS 042 or V08; 2) being an adult (18 years or older) at ARTs initiation; 3) receiving ARTs consisting of three or more antiretroviral medications including one of base agent of PIs, NNRTIs, or INSTIs; 4) having virologic and immunologic lab tests before the index date; and 5) having viral load reading before the index date. Patients were excluded if they had any evidence showing they would be treatment-experienced.[21] Evidence included: 1) viral load was less than 500 cells/mL any time before ARTs initiation; 2) initiated regimens included 5 or more agents or used a regimen containing 2 base agents ("5 or more agents" defined as there are 4 or more antiretroviral agents filled within ±15 days of the first fill of base agent; "2 base agents" defined as there was another base agent filled within 15 days after the first fill of base agent; 3) initiated ARTs was a single antiretroviral agent, defined

as no antiretroviral agent filled within ±30 days of the first fill of base agent; 4) received any antiretroviral agent earlier than 30 days before the first fill of base agent; or 5) the first fill of base agent was not 30 days of supply.

4.2 Variable Definition and Measurements

4.2.1 Exposure and Treatment Variables

The primary exposure variables were initial adherences, measured as the coverage ratio for the first fill of base agent and of complete regimen, respectively. Before estimating primary exposure variables, the relevant treatment variables were defined as follows.

The base agent variable was classified as unboosted PI, boosted PI, NNRTI, and INSTI, which was the same as the classification for the complete regimen. To differentiate unboosted PI and boosted PI, boosted PI was defined as the case that a patient has a fill of ritonavir within ±3 days of the first fill of a PI; otherwise, it was defined as unboosted PI. ARTs discontinuation was defined as when that patient did not have a second fill of base agent within 60 days after the index date, since the days of supply for the first fill of base agent was 30 days. Switching was defined as when patients changed their base agent from one class to another.

The initial coverage ratio (ICR) for the first fill of base agent (BA) was calculated according to the formula:

$$ICRBA = \frac{30\ days}{\begin{array}{c}Days\ difference\ between\ index\ date\ and\ the\ second\ fill\ date\ of base\ agent \\ or\ Day\ 60\ if\ no\ second\ fill\end{array}}. \quad (4.1)$$

If ICRBA was larger than 1, then it was converted to 1. The initial coverage ratio (ICR) for

the first fill of complete regimen (CR) was calculated according to the formula:

$$ICRCR = \frac{Days\ for\ complete\ regimen\ available\ in\ the\ period\ defined\ in\ the\ denominator}{Days\ difference\ between\ index\ date\ and\ the\ second\ fill\ date\ of\ base\ agent \\ or\ Day\ 60\ if\ no\ second\ fill}.$$

(4.2)

The complete regimen was defined as one base agent plus at least two other NRTIs.

The thereafter one-year adherence to ARTs was measured using the proportion of days covered (PDC) approach. The thereafter one-year PDC for BA was calculated as:

$$PDCBA = \frac{Days\ when\ base\ agent\ covered\ in\ 1\ year\ since\ second\ fill\ of\ base\ agent}{Days\ between\ the\ second\ fill\ date\ of\ base\ agent\ and \\ the\ end\ of\ 1-year\ follow-up}.$$

(4.3)

The thereafter one-year PDC for CR was calculated as:

$$PDCCR = \frac{Days\ when\ complete\ regimen\ covered\ in\ 1\ year\ since\ second\ fill\ of\ base\ agent}{Days\ between\ the\ second\ fill\ date\ of\ base\ agent\ and \\ the\ end\ of\ 1-year\ follow-up}.$$

(4.4)

If patients switched regimen class, then the observations at the switch date were censored.

The ICRs and PDCs were measured as continuous variables. For specific aims, these were transformed into binary variables using different thresholds or into categorical variables according to the sample size and clinically meaningful cutoffs.

4.2.2 Outcome Variables

The primary outcome was that first viral suppression occurred within thirty to 60 days after the first fill of base agent. The HIV treatment guidelines did not provide a specific definition for viral suppression. But the guidelines recommended to target a treatment goal of achieving an undetectable level of viral load, defined as <400 copies/mL in the guidelines of 1999 and <50 copies/mL since 2000.[80] It was also common to use ≥200/mL copies to define viral failure.[80] In this study, viral suppression was defined as HIV-1 RNA <400 copies/mL if test year was 1999 and HIV-1 RNA <50 copies/mL if test year was 2000 or after. In order to get the robust adherence effect estimate on virologic outcomes, sensitivity analyses for evaluating initial adherence effect on suppressing viral load to <50 copies/mL, < 200 copies/mL, and < 400 copies/mL were also conducted.

Since CD4 count is not responsive in such a short time period, thirty to 60 days, immunologic response was not considered in this study.

4.2.3 HIV Health Care Utilization Variables

Health care utilization at the individual level was estimated, including HIV office visits, length of stay (LOS) for hospitalization, viral load test frequency, and CD4 count test frequency during the one-year period after the index date.

4.2.4 Confounders and Other Covariates

Antiretroviral regimens with their relevant characteristics, including efficacy, side effects, and barriers to drug resistance, were associated with initial adherence and were

also risk factors related to virologic outcomes. However, they were not on the causal pathway between adherence and outcome. This indicated that regimens and their characteristics were important confounders, which made causality of initial adherence on virologic outcome complex. Therefore, this study was based on the subgroup of each specific regimen category, which negated the need to consider characteristics as a confounder.

As shown in Figure 4.1, confounders associated with initial adherence and virologic outcomes that were measured in this study included patient demographics (age, gender, and race/ethnicity), baseline HIV disease severity (baseline viral load, baseline CD4 count, and opportunistic infection, as defined in Table 4.1, and AIDS defined in Table 4.2), baseline overall health status (Deyo-adapted Charlson Comorbidity Index [CCI]), and HIV health care utilizations (length of stay [LOS], viral load test frequency, CD4 count test frequency, number of HIV office visits) during exposure period.

Other covariates include social economic status (SES), pill burden, and specific comorbid conditions. The specific comorbid conditions were defined in Table 4.3.

All variables with the anticipated variable formats were listed in Table 4.4.

4.3 Data Analyses

4.3.1 Data Analyses for Aim 1

Patient baseline characteristics including age, gender, race/ethnicity, socioeconomic status (SES), viral load, CD4 counts, initiated regimen, pill burden, Deyo-adpated CCI, and comorbid conditions were summarized for the entire cohort. Mean and standard deviation (STD) were calculated for continuous variables; number and proportion

were calculated for categorical variables.

Characteristics between patients initiated on different regimens were compared. Since there were four treatment groups to compare, one-way analysis of variance (ANOVA) tests were used for continuous variables regardless of data distribution, because one-way ANOVA is considered a robust test against the normality assumption. As for categorical variables, a Chi-square test or Fisher exact test were to make comparisons between groups, depending on whether the expected number for each cell of the variable is >5.

The proportion of patients who discontinued initiated regimen with 95% confidence interval of proportion was calculated for each initiated regimen category. For patients who discontinued regimen, their initial coverage ratio of base agent (ICRBA) was automatically calculated as 50%, because 30 days of supply were regarded to cover 60 days, which was the longest follow-up time that we measured for Aim 4. The mean and STD of ICRBA and initial coverage ratio of a complete regimen (ICRCR) for each initiated regimen category were calculated. The number and proportion of each class of ICRBA and ICRCR were also calculated.

The proportions including 95% confidence interval of patients who switched regimen category within one year from index date were calculated for each initiated regimen category. Mean, STD, and median for days gap between index date and date when patients switched initiated regimen category were also calculated. Switching pattern was displayed as proportion of patients who switched from a specific regimen category to another.

Finally, one-year proportion of days covered of base agent (PDCBA) and

proportion of days covered of a complete regimen (PDCCR) at individual level were used for analyses in Aim 3.

4.3.2 Data Analyses for Aim 2

Box and Whisker Plots were drawn for comparing the one-year HIV office visit frequency, LOS, viral load test frequency, and CD4 count test frequency among subgroups stratified by different categorical variables including initiated regimen, age, race/ethnicity, SES, baseline viral load, baseline CD4 count, and Deyo-adapted CCI.

4.3.3 Data Analyses for Aim 3

Pearson Correlation was calculated between ICRBA and ICRCR, ICRs and thereafter one-year PDCs for each initiated regimen category. The proportions of patients at each specific ICRCR category ≥95%, 75–<95%, or <75%) moving to specific thereafter one-year PDCCR category (≥95%, 75–<95%, or <75%) were also calculated. Figures were drawn to show adherence change pattern by initiated regime. Proportions of patients at ICRCR of ≥95%, 80–<95%, 65–<80%, 50–<65%, and <50% moving to specific thereafter one-year PDCCR category were displayed in the figure for each initiated regimen category. For each regimen category, Kappa coefficient between the ICRBA and one-year PDCCR was also calculated.

4.3.4 Data Analyses for Aim 4

The analyses for Aim 4 were the core part of this project. First, patients' baseline characteristics were compared at different ICRCR level (high: ≥95%, medium: 75–<95%,

and low: <75%) for each initiated regimen category via presenting mean with STD for continuous variables and number with proportion for categorical variables.

Second, patients who had virologic outcome data within thirty to 60 days after index date were compared to those who do not. Since there were only two groups, t-test was used to compare continuous variables, and Chi-square test was used for comparing categorical variables.

Third, data were imputed for patients who had missing virologic outcomes via multiple imputation methods to impute log value with base 10 of absolute viral load. In order to maximize the accuracy for imputing outcome, imputation was completed for each specific initiated regimen category by comparing two different imputation methods including monotone regression and Markov chain Monte Carlo (MCMC) method. The imputed outcome distribution derived from the two methods was compared with outcome distribution from the complete cases to identify the imputed data from one method which were more similar to the distribution of complete cases. The imputation model inputs were all variables that occurred before the outcome, including initiated pill burden, ICRCR, age, gender, race/ethnicity, SES, baseline viral load, baseline CD4 count, Deyo-adapted CCI, AIDS, opportunistic infection, specific comorbid conditions, discontinuation indicator, switch indicator, time to switch, viral load test frequency, CD4 test frequency, LOS, HIV office visit frequency, death within 60 days after index date, and index year.

Fourth, after the imputation, the crude viral suppression rate at different ICRCR category was compared based on completed cases and imputed data. Viral suppression rate among 4 groups were also compared (group 1: patients who did not discontinue and had virologic outcome within 30–60 days; group 2: patients who did not discontinue but had

missing outcome; group 3: patients who discontinued but had virologic outcome; and group 4: patients who discontinued and had missing outcome) based on the imputed date.

Fifth, the IPTW method was used to address confounding bias in this study. There were two types of categorical initial adherence variables: dichotomous and multilevel.

For dichotomous, the IPTW for each individual patient was calculated based on the following formula[79,81,82]:

$$\text{Numerator of IPTW: } \Pr(A = a_i | V = v_i) = \beta_1 * V,$$
$$\text{Denominator of IPTW: } \Pr(A = a_i | V = v_i, L = l_i) = \beta_1 * V + \beta_2 * L, \quad (4.5)$$

where *i* represents subject *i*; *A* is initial coverage ratio indicator (0 inadherent, 1 adherent); *a* is observed initial coverage ratio indicator; *L* is confounders; *V* is patient baseline characteristics except for confounders.

For multilevel one, the IPTW for each individual patient was calculated based on the following formula[79,81,82]:

$$\text{Numerator of IPTW: } \Pr(A = \ adherence\ category\ j \mid V = v_i) = \beta_1 * V,$$
$$\text{Denominator of IPTW: } \Pr(A = \ adherence\ category\ j \mid V = v_i, L = l_i) = \beta_1 * V + \beta_2 * L, \quad (4.6)$$

where *i* represents subject *i*; *j* is coverage ratio category: *j* = 1, 2, 3 with 1 = "≥95%", 2 = "75–<95%", 3 = "<75%", and we use 1 as the reference group; *A* is initial coverage ratio category; *a* is observed initial coverage ratio; *L* is confounders; *V* is patient baseline

characteristics except for confounders.

Sixth, viral suppression rate was calculated for each adherence group based on pseudo-population after weighting IPTW, and MSMs were calculated to estimate adherence effects on virologic outcomes.

For each initiated regimen category, confounders between adherence groups (inadherent vs. adherent; ICRCR ≥95% vs. 75-<95% and ICRCR ≥95% vs. <75%) were compared before and after applying IPTW via using absolute standardized difference estimate (0.1 as reference value). For each initiated regimen category, viral suppression rate was calculated for each adherence group after weighting IPTW. For each initiated regimen category, adherence effect on virologic outcomes was estimated via MSMs models.

When adherence variable was dichotomous one, then the model was

$$F(p(Y|V, L))= a*\beta_1 + V*\beta_2 \text{ (with weighting IPTW)}, \quad (4.7)$$

where *Y* is viral suppression outcome, *V* is baseline covariates, *L* is confounders, *a* is binary adherence, and *F* is the function (logistic regression to estimate odds ratios in this study).[79,81,82]

When adherence variable was multilevel one, then the model was

$$F(p(Y|V, L))= a_1*\beta_{11} + a_2*\beta_{12} + a_3*\beta_{13} + V*\beta_2 \text{ (with weighting IPW)}, \quad (4.8)$$

where *Y* is viral suppression outcome, *V* is baseline covariates, *L* is confounders, where

a_1=1 if ICRCR ≥95% and 0 otherwise, a_2=1 if ICRCR 75-<95% and 0 otherwise, a_3=1 if ICRCR <75% and 0 otherwise, and *F* is the function (logistic regression to estimate odds ratio in this study). [79,81,82]

Seventh, in order to obtain robust results, sensitivity analyses were conducted with multiple ways: 1) applying IPTW approach and building MSMs model based complete cases; 2) changing the definition of viral suppression including viral load <200 and <400 copies/mL, respectively.

Table 4.1 ICD-9 Diagnosis Codes for Opportunistic Infections According to the Center for Disease Control and Prevention (CDC) Definition[83]

Comorbidity	ICD-9 Code(s)
Pneumocystis jirovecii pneumonia	136.3
Toxoplasmosis of brain, onset at age >1 month†	130.0
Cryptosporidiosis, chronic intestinal (>1 month's duration)	007.4
Microsporidiosis	136.8
Mycobacterium avium complex or Mycobacterium kansasii, or other species; disseminated or extrapulmonary	031.XX
Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary	010-018
Bacterial pneumonia	481, 482.XX
Bartonellosis	088.0
Syphilis	091.XX, 092.X, 093.XX, 094.XX, 097.X, 096
Mucocutaneous candidiasis	112.0, 112.2, 112.3, 112.4, 112.5, 112.8X, 112.9
Cryptococcosis, extrapulmonary	321.0
Histoplasmosis, disseminated or extrapulmonary	115.XX
Coccidioidomycosis, disseminated or extrapulmonary	114.1, 114.2, or 114.3
Aspergillosis	117.3, 484.6, 518.6
Cytomegalovirus	078.5
Herpes simplex virus disease	054.XX
Varicella zoster virus disease	053.XX
Human papillomavirus disease	079.4, 795.05, 795.09, 795.15, 795.19
Hepatitis B infection	070.2X, 070.3X
Hepatitis C infection	070.41, 070.44, 070.51, 070.54, 070.7X
Progressive multifocal leukoencephalopathy	046.3
Malaria	084.X
Leishmaniasis	085.X
Chagas Disease	086.X
Isosporiasis	007.2

Table 4.2 ICD-9 Diagnosis Codes for AIDS Conditions According to the Center for Disease Control and Prevention (CDC) Definition [84]

Comorbidity	ICD-9 Code(s)
Candidiasis of bronchi, trachea, or lungs	112.4
Candidiasis of esophagus	112.84
Cervical cancer, invasive	180.X
Coccidioidomycosis, disseminated or extrapulmonary	114.1, 114.2, 114.3
Cryptococcosis, extrapulmonary	321.0
Cryptosporidiosis, chronic intestinal (>1 month's duration)	007.4
Cytomegalovirus	078.5
Herpes simplex: chronic ulcers or bronchitis, pneumonitis, or esophagitis	054.XX
Histoplasmosis, disseminated or extrapulmonary	115.XX
Isosporiasis	007.2
Kaposi sarcoma	176.XX
NonHodgkin's Lymphoma, including Burkitt's, immunoblastic, or primary of brain (or equivalent term)	200.XX, 202.0X, 202.1X, 202.2X, 202.7X, 202.8X, 204.1X
Mycobacterium avium complex or Mycobacterium kansasii, or other species; disseminated or extrapulmonary	031.XX
Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary	010-018
Pneumocystis jirovecii pneumonia	136.3
Pneumonia, recurrent	V12.61
Progressive multifocal leukoencephalopathy	046.3
Salmonella septicemia, recurrent	003.1
Toxoplasmosis of brain, onset at age >1 month†	130.0
Wasting syndrome attributed to HIV (cachexia)	799.4

Table 4.3 List of Comorbid Conditions with ICD-9-CM Codes

Comorbid Condition	ICD-9-CM Codes
Cancer	140-175, 177-239
Cardiac arrhythmias	427
Diabetes	250
Hypertension	401-405
Hyperlipidemia	272
Ischemic heart diseases, angina	401-414
Cardiac insufficiency	428-429
Heart valve diseases	424
Cerebrovascular disease	430-438
Chronic obstructive pulmonary disease	491.1, 491.20, 491.21, 491.9, 496, 492.0, 492.8
Osteoarthritis	715-716
Chronic anemias, autoimmune, hemolytic	280, 281, 282.0, 283-4, 285.0
Renal insufficiency	585-6
Depression	296.2X, 296.3X, or 296.82
Schizophrenic disorder	295.XX
Psychotic	298.8, 297.3, 293.81, 293.82, 298.9
Alcohol abuse	305.0X, 303.0, 303.9, 291.XX
Drug abuse	292.XX, 304.XX, 305.XX
Hepatitis B Infection	070.2X, 070.3X
Hepatitis C Infection	070.41, 070.44, 070.51, 070.54, 070.7X

Table 4.4 Variables with Anticipated Variable Formats

Variables	Variable Format
Treatment Variables	
Regimen/Base agent	Categorical (Unboosted PI, Boosted PI, NNRTI, INSTI)
Discontinuation	Dichotomous (yes or no)
Switch	Dichotomous (yes or no)
Exposure Variables	
ICACA	Ratio; Categorical based on distribution; Dichotomous (using different threshold at 95%, 90%, 85%, 80%, 75%)
ICACR	Ratio; Categorical based on distribution; Dichotomous (using different threshold at 95%, 90%, 85%, 80%, 75%)
Other Adherence Variables	
Thereafter one-year PDCBA	Ratio
Thereafter one-year PDCCR	Ratio
Health Care Utilization Variables	
HIV office visit frequency in one year	Count
LOS in one year	Count
Viral load test in one year	Count
CD4 count test in one year	Count
Outcome Variables	
Viral suppression (viral load <50 copies/mL)	Dichotomous (yes or no)
Viral load <200 copies/mL	Dichotomous (yes or no)
Viral load <400 copies/mL	Dichotomous (yes or no)

Table 4.4 Continued

Variables	Variable Format
Confounders	
Age	Continuous or categorical (18–35, 36–50, 51–65, >65)
Gender	Dichotomous (male or female)
Race/Ethnicity	Categorical (White, African-American, Hispanic, others, and unknown)
Baseline viral load	Continuous or categorical (<10,000, 10,000–<50,000, 50,000–<100,000 100,000–<500,000, ≥500,000)
Baseline CD4 count	Continuous or categorical (<200, 200–499, ≥500, and unknown)
AIDS	Dichotomous (yes or no)
Opportunistic infection	Dichotomous (yes or no)
Deyo-adapted CCI	Continuous or categorical (0, 1–2, ≥3)
LOS during exposure period	Count
HIV office visit frequency during exposure period	Count
Viral load tests during exposure period	Count
CD4 count tests during exposure period	Count
Covariates	
Social Economic Status	Categorical based on distribution
Comorbid conditions	Dichotomous (yes or no) for each specific comorbid condition
Pill burden (single pill per day)	Dichotomous (yes or no)

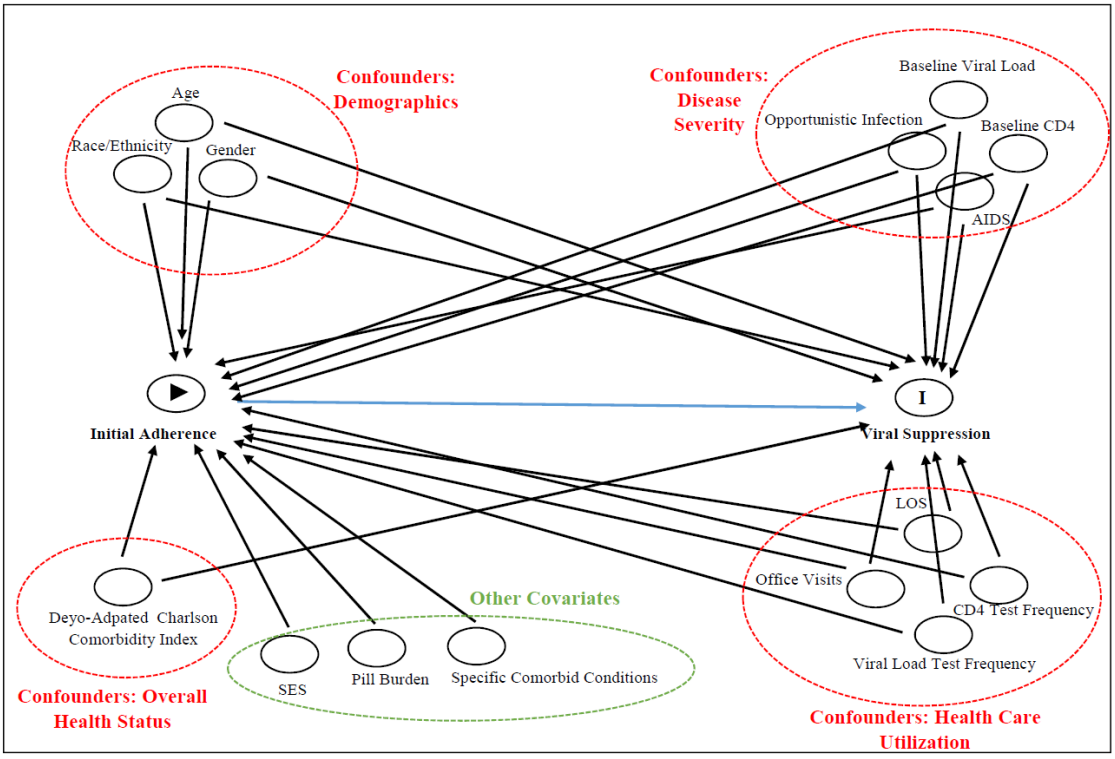


Figure 4.1 Directed Acyclic Graph for Initial Adherence and Viral Suppression

CHAPTER 5

RESULTS

5.1 Results for Aim 1

5.1.1 Cohort Selection

A total of 53,427 veterans with at least one diagnosis of HIV-1 or AIDS from 1999 to2015 were identified from the VHA databases, and of those, 34,598 patients were treated with ARTs. After executing inclusion/exclusion criteria, a total of 10,274 veterans remained in the final cohort. The detailed process of selecting the cohort is shown in Figure 5.1.

5.1.2 Cohort Characteristics

As shown in Tables 5.1 and 5.2, the cohort were relatively young with a mean age of 47.3 years old; the majority were younger than 65 years old at baseline. More than half were African-Americans, and about 29% were whites. A total of 36.6% veterans reached a very high level of viral load ≥100,000 copies/mL when they initiated the ARTs. About 9.3% veterans initiated the ARTs with a higher than normal (≥500 cells/mL) CD4 count level. Among the cohort, 17.7% and 25.3% patients had AIDS conditions and opportunistic infections at the baseline, respectively. There were 976 (9.5%), 2291 (22.3%), 6,374 (62.0%), and 633 (6.2%) patients initiated on unboosted PIs, boosted PIs, NNRTIs, and

INSTIs, respectively. One-third of patients were treated on single-pill ARTs. About 44.2% patients had no comorbid conditions. The most frequent comorbid conditions were drug abuse, ischemic heart disease, alcohol abuse, and hypertension, with the prevalence being 48.6%, 30.1%, 29.6%, and 28.6%.

Baseline characteristics among patients initiated with different regimens were also analyzed (Table 5.3). Patients initiated with boosted PIs had older mean age compared to the others; however, patients on INSTIs had the highest proportion of elderly aged over 65 year old. Whites were more likely to be treated on INSTIs, while African-Americans were less likely to be treated on INSTIs. Patients at a higher SES status were more likely on INSTIs; in comparison, those at a lower SES were more likely to be on PI-based regimens. Patients initiated with unboosted PIs had the lowest mean level of viral load, followed by NNRTIs, INSTIs, and boosted PIs. Patients initiated with INSTIs had the highest mean level of CD4 counts, followed by NNRTIs, unboosted PIs, and boosted PIs. Patients initiated with boosted PIs had a higher proportion of AIDS conditions and opportunistic infections than patients on the other regimens. In comparison, patient on INSTIs had less severe HIV disease. No patients on PI-based regimens were treated on a single pill of ARTs. About 49.7% and 40.9% patients were on a single pill of NNRTI- and INSTI-based regimens, respectively. Patients on unboosted PIs had the least comorbid conditions, while patients on INSTIs had the most. A detailed comparison is included in Table 5.3.

5.1.3 Patients' Refill Pattern

There were 1,678 (16.3%) and 504 (4.9%) patients who did not have a second fill in 60 days or one year since the index date, respectively. The proportion of patients who

discontinued the initiated regimen in 60 days since the index date is displayed in Figure 5.2. Patients initiated on unboosted PIs had the highest discontinuation rate of 20.9%, compared to boosted PIs of 17.4%, NNRTIs of 15.9%, and INSTIs of 10.1%.

There were 8,596 patients who did not discontinue the ARTs within 60 days with the mean of 29.6±9.7 days for days gap between the first and second fill of base agent. Among them, 5,469 (63.6%) patients had second fill within 30 days with the mean of 23.8±4.5 days for days gap.

Patients initiated with unboosted PIs had the lowest initial coverage ratio with ICRBA of 0.84 and ICRCR of 0.83. Patients initiated with INSTIs had the highest initial coverage with ICRBA of 0.90 and ICRCR of 0.89. The detailed results may be found in Table 5.4. More than 50% of patients had both ICRBA and ICRCR ≥95% across all the regimens. However, there was still a proportion of patients with a very low level of ICRBA and ICRCR at <65%, with the proportion range of 14.7% to 28.5%.

A total of 1,502 (14.6%) patients switched their initiated regimen in one year since the index date. The switching rate distribution across the initiated regimens is shown in Figure 5.3. About 25.8% patients initiated on unboosted PIs switched to another regimen category, followed by 19.2% for boosted PIs, 12.0% for NNRTIs, and 7.1% for INSTIs.

The days between the index date and the date when the switching occurred across the initiated regimens were also calculated (Figure 5.4 and Table 5.5). The distribution of days is similar among the regimens with the range for means of 162 to 165 days. When comparing the median days, patients initiated boosted PIs switched earlier than other regimens, then NNRTIs, unboosted PIs, and INSTIs.

As shown in Figure 5.5, patients initiated with unboosted PIs primarily switched to

boosted PIs or NNRTIs; patients initiated with boosted PIs primarily switched to unboosted PIs or NNRTIs, and a small proportion switched to INSTI; patients initiated with NNRTIs primarily switched to boosted PIs, and a small proportion switched to unboosted PIs or INSTIs; patients initiated with INSTIs primarily switched to NNRTIs or boosted PIs. Across all initiated regimens, a few patients switched to a regimen composed of two base agents.

5.1.4 Thereafter One-Year Adherence

Patients were censored when they switched their initiated regimens. There were 171 patients who switched regimen on the second fill, so they were excluded for calculating thereafter one-year PDC. Similar to the pattern for ICRs, patients on INSTIs had the highest PDCBA and PDCCR, followed by NNRTI, boosted PI, and unboosted PI. The results are shown in Table 5.6.

5.2 Results for Aim 2

5.2.1 HIV Health Care Utilization

The mean viral load monitoring frequency in one year after the index date was about 3.3 ± 1.8, whereas the mean CD4 count monitoring frequency was about 2.5 ± 2.0. Patients' HIV office visits were about 7.9 ± 6.9 times on the average in one year after the index date. About 21.6% patients were hospitalized during one year, with the mean length of stay about 20.2 days. The Box and Whisker Plots for distribution of viral load monitoring frequency, CD4 count test frequency, HIV office visits, and LOS between subgroups by different characteristics are displayed in Figures 5.6–5.10. Little to no difference was found

across these subgroups for each health care utilization variable.

5.3 Results for Aim 3

5.3.1 Relationship between ICRs and PDCs

The correlation between initial coverage ratio of base agent and of complete regimen was very strong, with the correlation estimate in the range of 0.92–0.96 for various initiated regimens. However, the correlations between ICRs and thereafter one-year PDCs were medium with the estimate in the range of 0.54–0.63. The correlation estimates are included in Tables 5.7 and 5.8.

Patients on unboosted PIs were more likely to move to a lower adherence level than the others. In comparison, patients on INSTIs were more likely to move to a higher adherence level than the others. The patterns of patients changing adherence level is shown in Table 5.9 and Figure 5.11. The Kappa coefficients shown in Table 5.10 were also calculated to estimate the inter-rater agreements between initial coverage ratio of base agent and thereafter one-year PDC of complete regimen based on the categories classified in Figure 5.11. The Kappa coefficients indicated a fair strength of the agreements, since all coefficients were in the range of 0.21-0.40.[85]

5.4 Results for Aim 4

5.4.1 Patient Characteristics Comparison at Different Adherence Level

Patient characteristics at different adherence level were calculated for each initiated regimen category (Tables 5.11-5.14). They consistently show that the patients most likely to exhibit poor adherence were African-American, with lower SES, at lower baseline viral

load, and higher CD4 counts for all initiated regimens. For other characteristics, patients with poor adherence and treated with unboosted PIs were those who were younger, male, had less severe HIV conditions, and less comorbidity; patients with poor adherence and treated with boosted PIs were those who were older, female, had more severe HIV conditions, and less comorbidity; patients with poor adherence and treated with NNRTIs were those who were older, female, with more severe HIV conditions, and more comorbidity; patients with poor adherence and treated with INSTIs were those who were younger, female, with less severe HIV conditions, and less comorbid.

5.4.2 Patients Characteristics Comparison on Outcome Missing

There were 5,955 (58.0%) patients who did not have records for virologic outcomes within thirty to 60 days of the index. We compared them to patients who did have virologic outcomes. We find that patients with missing outcomes were those who were younger, African-American, at lower baseline viral load and higher baseline CD4 counts, treated on PIs, healthier, and at lower adherence level. The results are shown in Table 5.15.

5.4.3 Missing Outcome Imputation

In order to avoid selection bias, both patients with and without outcomes in the study were included. The outcome for patients who had missing value were imputed. The data distributions for viral load in log10 were also compared before and after imputation for each specific regimen category as shown in the Figure 5.12. The outcome distribution before and after imputation are very similar for each specific regimen category.

The distribution of viral suppression rate was compared by the change of adherence

before and after imputation (Figure 5.13). The distributions were based on crude estimates without controlling patient characteristics. Due to this reason, although the overall trend was that decreased adherence is associated with decreased viral suppression rate, the viral suppression rate was waving. In general, patients on INSTIs had the highest viral suppression rate, followed by patients on NNRTI, unboosted PI, and boosted PIs.

Patients were divided into four groups: Group 1—patients who had both second fill within 60 days and viral load test within 30–60 days; Group 2—patients who had only second fill within 60 days but no viral load test within 30–60 days; Group 3—patients who had viral load test within 30–60 days but no only second fill within 60 days; and Group 4—patients who neither had second fill within 60 days nor had viral load within 30–60 days. Since Group 2 and Group 4 had missing virologic outcome, the viral suppression rate was based on imputed date for these two groups. The viral suppression rate for Group 2 and Group 4 was observed to be lower than that for Group 1 and Group 3, respectively, except for patients on INSTIs. This might be caused by the fairly small sample size in Group 2 for patients on INSTIs (Figure 5.14).

5.4.4 Results Based on Adherence as Dichotomous Variable

An IPTW approach to create pseudo-populations was used to remove biases caused by the confounders based on data for each specific regimen category. The absolute standardized differences (ASD) for each confounder was compared before and after weighting data. As shown in Figure 5.15, all confounders became balanced after the IPTW was applied to each specific regimen model, except for INSTIs data, where the ASD for "unknown CD4 count" was still higher than 0.1.

Based on the weighted data, viral suppression rate was estimated for patients who were adherent vs. nonadherent. The results are displayed in Figure 5.16. Across all regimens, regardless of selected cutoff to define adherence, the viral suppression rate among patients at adherence level above the cutoff was similar. For example, viral suppression rate among patients who were adherent to unboosted PIs was estimated to be 15.0–16.5%, with 12.5–13.4% for boosted PIs, 21.2–21.8% for NNRTIs, and 50.4–51.4% for INSTIs. However, when the viral suppression rate difference between adherent patients vs. nonadherent patients was compared, the 85% cutoff could be meaningful for other cutoffs among patients on unboosted PIs, since the cutoff lower than 85% did not much change the viral suppression rate for nonadherent patients. But for other regimens, the change of viral suppression rate among nonadherent patients by changing cutoff was somewhat linearly associated. Interestingly, although adherent patients on unboosted PIs and boosted PIs had very similar viral suppression rate, the nonadherent patients on boosted PIs had better outcome than those on unboosted PIs. In comparison, patients on INSTIs had the best viral suppression rate regardless of adherence level, and patients on NNRTIs could also achieve better viral suppression rate than patients on PIs.

In the MSM models, adherence had the biggest effect on viral suppression among patients on unboosted PIs, followed by boosted PIs, INSTIs, and NNRTIs. The results are shown in Table 5.16. For example, among pseudo-population initiated with unboosted PIs, patients with initial coverage ratio of ≥ 95% were 3 times (calculated as 1/0.33=3) more likely to achieve viral suppression in thirty to 60 days than those with coverage ratio of <95%; patients with initial coverage ratio of ≥ 75% were 5.6 times (calculated as 1/0.18=5.6) more likely to achieve viral suppression in thirty to 60 days than those with

coverage ratio of <75%. In comparison, among pseudo-population initiated with INSTIs, patients with initial coverage ratio of ≥ 95% were 2.3 times (calculated as 1/0.44=2.3) more likely to achieve viral suppression in thirty to 60 days than those with coverage ratio of <95%; those with initial coverage ratio of ≥ 75% were 3.8 times (calculated as 1/0.26=3.8) more likely to achieve viral suppression in thirty to 60 days than those with coverage ratio of <75%.

5.4.5 Results Based on Adherence as Multilevel Variable

The ASDs for each confounder before and after weighting data by comparing patients at adherence 75-<95% vs. ≥95% and <75% vs. ≥95% are shown in Figure 5.17. The confounders become balanced after IPTW weighting, except for both comparisons for INSTIs and adherence <75% vs. ≥95% comparison for unboosted PIs.

In the MSM models, adherence had the biggest effect on viral suppression among patients on PI-based regimens. The results are shown in Table 5.17. Regardless of regimen, adherence at 75-<95% did not have a statistically significant effect on viral suppression rate compared to adherence at ≥95%; however, these differences might still be clinically significant. For example, among pseudo-population initiated with unboosted PIs, patients with initial coverage ratio of ≥ 95% were 1.6 times (calculated as 1/0.63=1.6) more likely to achieve viral suppression in thirty to 60 days than those with coverage ratio of 75-<95%; patients with initial coverage ratio of ≥ 95% were 7.7 times (calculated as 1/0.13=7.7) more likely to achieve viral suppression in thirty to 60 days than those with coverage ratio of <75%. In comparison, among pseudo-population initiated with INSTIs, patients with initial coverage ratio of ≥ 95% were 1.1 times (calculated as 1/0.89=1.1) more likely to

achieve viral suppression in thirty to 60 days than those with coverage ratio of 75-<95%; those with initial coverage ratio of ≥ 95% were 4 times (calculated as 1/0.25=4) more likely to achieve viral suppression in thirty to 60 days than those with coverage ratio of <75%.

5.4.6 Sensitivity Analysis

Viral suppression rate of patients at different adherence levels were compared between various regimens in Figure 5.18. Patients with adherence ≥95% to INSTIs had the highest rate of suppression (50.9%), followed by 21.3% for NNRTIs, 16.3% for unboosted PI, and 13.2% for boosted PI. When viral suppression rate of patients at adherence 75–<95% and ≥95% were compared, the viral suppression rate dropped by 33.1%, 33.3%, 11.3%, and 5.8% for unboosted PIs, boosted PIs, NNRTIs, and INSTIs, respectively. INSTIs performed best, because patients with adherence <75% still had a viral suppression rate of 20.7%.

Sensitivity analyses were also conducted using the following methods: 1) analysis based on patients who did not have missing virologic outcomes; and 2) analysis based on using viral load <200 and <400 copies/mL as the outcome, respectively. The results are included in the Appendix. The findings are similar to the primary analyses.

Table 5.1 Patient Baseline Characteristics among HIV Treatment-Naïve Veterans

	Mean/N	SD/%
Demographics		
Age	47.3	10.9
18–35 years old	1571	15.3%
36–50 years old	4605	44.8%
51–65 years old	3672	35.7%
>65 years old	426	4.1%
Male	9921	96.6%
Race/Ethnicity		
White	2972	28.9%
African-American	5684	55.3%
Hispanic	664	6.5%
Others	119	1.2%
Unknown	835	8.1%
Social Economic Status (Low to High)		
1st Quartile	2290	22.3%
2nd Quartile	2264	22.0%
3rd Quartile	2276	22.2%
4th Quartile	2278	22.2%
Unknown	1166	11.3%
Baseline Labs		
Viral Load (1000 copies/mm3)	176.5	520.1
<10,000	2032	19.8%
10,000–<50,000	2683	26.1%
50,000–<100,000	1791	17.4%
100,000–<500,000	2849	27.7%
≥500,000	919	8.9%
CD4 Counts (cells/mm3)	266.7	212.5
<200	3244	31.6%
200–499	3495	34.0%
≥500	954	9.3%
Unknown	2581	25.1%
Disease Severity		
AIDS	1814	17.7%
Opportunistic Infection	2598	25.3%
Initiated Regimen		
Regimen		
Unboosted PI	976	9.5%
Boosted PI	2291	22.3%
NNRTI	6374	62.0%
INSTI	633	6.2%
All agents in a single pill	3427	33.4%

Table 5.2 Patient Baseline Comorbidities among HIV Treatment-Naïve Veterans

	Mean/N	SD/%
Deyo-adapted Charlson Comorbid Index	2.2	3.0
Deyo-adapted CCI=0	4540	44.2%
Deyo-adapted CCI=1 or 2	2788	27.1%
Deyo-adapted CCI≥3	2946	28.7%
Comorbid Conditions		
Hepatitis B	726	7.1%
Hepatitis C	1913	18.6%
Alcohol Abuse	3043	29.6%
Drug Abuse	4997	48.6%
Depression	1782	17.3%
Schizophrenic Disorder	575	5.6%
Psychotic	556	5.4%
Cancer	1167	11.4%
Cardiac Arrhythmias	312	3.0%
Diabetes	874	8.5%
Hypertension	2941	28.6%
Hyperlipidemia	1630	15.9%
Ischemic Heart Disease	3092	30.1%
Cardiac Insufficiency	303	2.9%
Heart Valve Disease	102	1.0%
Cerebrovascular Disease	256	2.5%
COPD	589	5.7%
Osteoarthritis	1155	11.2%
Chronic Anemias	468	4.6%
Renal Insufficiency	468	4.6%

Table 5.3 Baseline Characteristics among Patients Initiated with Different Regimen

	Unboosted PI (N=976)		Boosted PI (N=2,291)		NNRTI (N=6,374)		INSTI (N=633)		P-value
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	
Age	46.5	9	47.9	10.5	47.3	11	47	13.2	0.0038
18–35 years old	105	10.8%	306	13.4%	1008	15.8%	152	24.0%	<0.0001
36–50 years old	561	57.5%	996	43.5%	2833	44.4%	215	34.0%	
51–65 years old	290	29.7%	910	39.7%	2250	35.3%	222	35.1%	
>65 years old	20	2.0%	79	3.4%	283	4.4%	44	7.0%	
Male	957	98.1%	2213	96.6%	6151	96.5%	600	94.8%	0.0055
Race/Ethnicit White	261	26.7%	647	28.2%	1855	29.1%	209	33.0%	0.0187
African-American	534	54.7%	1274	55.6%	3549	55.7%	327	51.7%	
Hispanic	70	7.2%	136	5.9%	413	6.5%	45	7.1%	
Others	11	1.1%	33	1.4%	64	1.0%	11	1.7%	
Unknown	100	10.2%	201	8.8%	493	7.7%	41	6.5%	
SES 1st Quartile	228	23.4%	526	23.0%	1412	22.2%	124	19.6%	0.0019
2nd Quartile	217	22.2%	503	22.0%	1389	21.8%	155	24.5%	
3rd Quartile	198	20.3%	484	21.1%	1431	22.5%	163	25.8%	
4th Quartile	199	20.4%	494	21.6%	1440	22.6%	145	22.9%	
Unknown	134	13.7%	284	12.4%	702	11.0%	46	7.3%	
Viral Load (1000 copies/mm^3)	140.9	211.7	225.8	601.1	159.5	483.2	223.8	804.7	<0.0001
<10,000	210	21.5%	399	17.4%	1284	20.1%	139	22.0%	<0.0001
10,000–<50,000	233	23.9%	531	23.2%	1724	27.0%	195	30.8%	
50,000–<100,000	190	19.5%	354	15.5%	1151	18.1%	96	15.2%	
100,000–<500,000	246	25.2%	726	31.7%	1723	27.0%	154	24.3%	
≥500,000	97	9.9%	281	12.3%	492	7.7%	49	7.7%	

Table 5.3 Continued

	Unboosted PI (N=976)		Boosted PI (N=2,291)		NNRTI (N=6,374)		INSTI (N=633)		P-value
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	
CD4 Counts (cells/mm^3)	244	211.2	229.7	208.2	272.1	204.8	371.9	259.7	<0.0001
<200	358	36.7%	855	37.3%	1899	29.8%	132	20.9%	<0.0001
200–499	288	29.5%	614	26.8%	2368	37.2%	225	35.5%	
≥500	83	8.5%	163	7.1%	580	9.1%	128	20.2%	
Unknown	247	25.3%	659	28.8%	1527	24.0%	148	23.4%	
AIDS	153	15.7%	448	19.6%	1100	17.3%	113	17.9%	0.0290
Opportunistic Infection	225	23.1%	662	28.9%	1592	25.0%	119	18.8%	<0.0001
All agents in a single pill	0	0.0%	0	0.0%	3168	49.7%	259	40.9%	<0.0001
Deyo-adapted CCI	1.7	2.7	2.4	3.2	2.1	2.9	2.6	3.3	<0.0001
Hepatitis B	56	5.7%	162	7.1%	474	7.4%	34	5.4%	0.0813
Hepatitis C	198	20.3%	494	21.6%	1134	17.8%	87	13.7%	<0.0001
Alcohol Abuse	240	24.6%	739	32.3%	1858	29.1%	206	32.5%	<0.0001
Drug Abuse	388	39.8%	1194	52.1%	3084	48.4%	331	52.3%	<0.0001
Depression	127	13.0%	471	20.6%	1008	15.8%	176	27.8%	<0.0001
Diabetes	60	6.1%	175	7.6%	564	8.8%	75	11.8%	0.0002
Hypertension	166	17.0%	656	28.6%	1880	29.5%	239	37.8%	<0.0001
Hyperlipidemia	46	4.7%	320	14.0%	1080	16.9%	184	29.1%	<0.0001
Ischemic Heart Disease	186	19.1%	693	30.2%	1971	30.9%	242	38.2%	<0.0001

Table 5.4 Initial Coverage Ratio among Treatment-Naïve Patients

	Unboosted PI (N=976)		Boosted PI (N=2,291)		NNRTI (N=6,374)		INSTI (N=633)	
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%
ICR of Base Agent	0.84	0.20	0.86	0.19	0.87	0.19	0.90	0.17
50–64%	264	27.1%	506	22.1%	1301	20.4%	93	14.7%
65–79%	66	6.8%	174	7.6%	470	7.4%	38	6.0%
80–94%	141	14.5%	256	11.2%	758	11.9%	77	12.2%
≥95%	505	51.7%	1335	59.1%	3845	60.3%	425	67.1%
ICR of Complete Regimen	0.83	0.21	0.85	0.21	0.86	0.20	0.89	0.18
<50%	22	2.3%	48	2.1%	56	0.9%	9	1.4%
50–64%	256	26.2%	487	21.3%	1290	20.2%	92	14.5%
65–79%	62	6.4%	180	7.9%	472	7.4%	36	5.7%
80–94%	143	14.7%	256	11.2%	754	11.8%	81	12.8%
≥95%	495	50.5%	1320	57.6%	3802	59.7%	415	65.6%

Table 5.5 Days Switch among Patients Who Switched Initiated Regimen

First Regimen	N	Mean Days (SD)	Median Days
Unboosted PI	252	165 (101)	160.5
Boosted PI	441	162 (98)	149
NNRTI	764	169 (100)	155
INSTI	45	165 (98)	167

Table 5.6 Thereafter One-Year Proportion of Days Covered among Treatment-Naïve Patients

	Unboosted PI (N=945)		Boosted PI (N=2,233)		NNRTI (N=6,295)		INSTI (N=630)		P-value
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	
One-Year PDC (Base Agent)	0.63	0.34	0.71	0.33	0.74	0.32	0.80	0.28	<0.0001
<50%	331	35.0%	558	25.0%	1424	22.6%	102	16.2%	<0.0001
50–64%	90	9.5%	206	9.2%	409	6.5%	37	5.9%	
65–79%	110	11.6%	205	9.2%	607	9.6%	49	7.8%	
80–94%	170	18.0%	456	20.4%	1240	19.7%	145	23.0%	
≥95%	244	25.8%	808	36.2%	2615	41.5%	297	47.1%	
One-Year PDC (Complete Regimen)	0.60	0.34	0.69	0.33	0.73	0.33	0.79	0.29	<0.0001
<50%	358	37.9%	624	27.9%	1522	24.2%	111	17.6%	<0.0001
50–64%	119	12.6%	211	9.5%	449	7.1%	37	5.9%	
65–79%	106	11.2%	224	10.0%	614	9.8%	52	8.3%	
80–94%	162	17.1%	456	20.4%	1243	19.8%	146	23.2%	
≥95%	200	21.2%	718	32.2%	2467	39.2%	284	45.1%	

Table 5.7 Pearson Correlations between Initial Coverage Ratio of Base Agent and Initial Coverage Ratio of Complete Regimen

First Regimen	Pearson Correlation	Initial Coverage Ratio (Complete Regimen)
Unboosted PI	Initial Coverage Ratio (Base Agent)	0.95
Boosted PI	Initial Coverage Ratio (Base Agent)	0.92
NNRTI	Initial Coverage Ratio (Base Agent)	0.96
INSTI	Initial Coverage Ratio (Base Agent)	0.94

Table 5.8 Pearson Correlations between Initial Coverage Ratio and Thereafter One-Year Proportion of Days Covered

First Regimen	Pearson Correlation	Thereafter One-Year PDC (Base Agent)	Thereafter One-Year PDC (Complete Regimen)
Unboosted PI	Initial Coverage Ratio (Base Agent)	0.60	0.58
	Initial Coverage Ratio (Complete Regimen)	0.56	0.56
Boosted PI	Initial Coverage Ratio (Base Agent)	0.63	0.61
	Initial Coverage Ratio (Complete Regimen)	0.60	0.61
NNRTI	Initial Coverage Ratio (Base Agent)	0.60	0.60
	Initial Coverage Ratio (Complete Regimen)	0.58	0.58
INSTI	Initial Coverage Ratio (Base Agent)	0.58	0.58
	Initial Coverage Ratio (Complete Regimen)	0.54	0.56

Table 5.9 Relationship between Initial Coverage Ratio and Thereafter One-Year Proportion of Days Covered

Initial Coverage Ratio (complete Regimen)	One-Year PDC (complete Regimen)	Proportions			
		Unboosted PI	Boosted PI	NNRTI	INSTI
≥95%	≥95%	32.3%	45.8%	53.8%	57.6%
	75–<95%	23.7%	26.7%	24.1%	26.8%
	<75%	44.0%	27.5%	22.2%	15.7%
75–<95%	≥95%	14.6%	21.4%	30.0%	31.1%
	75–<95%	30.3%	27.9%	29.9%	35.6%
	<75%	55.2%	50.8%	40.0%	33.3%
<75%	≥95%	5.4%	6.8%	9.1%	13.3%
	75–<95%	9.4%	11.7%	16.8%	18.0%
	<75%	85.2%	81.5%	74.1%	68.8%

Table 5.10 Inter-Rater Agreement between Initial Coverage Ratio of Base Agent and Thereafter One-Year PDC of Complete Regimen

Initiated Regimen	Kappa Coefficient	95% Confidence Interval
Unboosted PI	0.26	0.23-0.29
Boosted PI	0.31	0.29-0.34
NNRTI	0.33	0.31-0.35
INSTI	0.33	0.28-0.38

Table 5.11 Baseline Characteristics at Different Adherence among Patient on Unboosted PIs

	Patients at initial coverage ratio of complete regimen ≥ 95% (N=493)		Patients at initial coverage ratio of complete regimen 75–<95% (N=166)		Patients at initial coverage ratio of complete regimen <75% (N=328)	
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%
Age	46.7	9.1	46.6	8.3	46.1	9.2
18–35 years old	47	9.8%	19	11.4%	39	11.9%
36–50 years old	281	58.3%	87	52.4%	193	58.8%
51–65 years old	142	29.5%	59	35.5%	89	27.1%
>65 years old	12	2.5%	1	0.6%	7	2.1%
Male	470	97.5%	164	98.8%	323	98.5%
Race/Ethnicity White	156	32.4%	41	24.7%	64	19.5%
African-American	249	51.7%	98	59.0%	187	57.0%
Hispanic	21	4.4%	13	7.8%	36	11.0%
Others	5	1.0%	3	1.8%	3	0.9%
Unknown	51	10.6%	11	6.6%	38	11.6%
SES 1st Quartile	107	22.2%	40	24.1%	81	24.7%
2nd Quartile	111	23.0%	32	19.3%	74	22.6%
3rd Quartile	99	20.5%	38	22.9%	61	18.6%
4th Quartile	103	21.4%	33	19.9%	63	19.2%
Unknown	62	12.9%	23	13.9%	49	14.9%
Viral Load (1000 copies/mm3)	151.9	222.9	155.3	221.1	117.5	187.1
<10,000	91	18.9%	38	22.9%	81	24.7%
10,000–<50,000	105	21.8%	43	25.9%	85	25.9%
50,000–<100,000	104	21.6%	20	12.0%	66	20.1%
100,000–<500,000	128	26.6%	45	27.1%	73	22.3%
≥500,000	54	11.2%	20	12.0%	23	7.0%

Table 5.11 Continued

	Patients at initial coverage ratio of complete regimen ≥ 95% (N=493)		Patients at initial coverage ratio of complete regimen 75–<95% (N=166)		Patients at initial coverage ratio of complete regimen <75% (N=328)	
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%
CD4 Counts (cells/mm3)	244.9	209.4	219.9	183.3	254.9	226.4
<200	174	36.1%	62	37.3%	122	37.2%
200–499	141	29.3%	51	30.7%	96	29.3%
≥500	40	8.3%	13	7.8%	30	9.1%
Unknown	127	26.3%	40	24.1%	80	24.4%
All agents in a single pill	0	0.0%	0	0.0%	0	0.0%
Deyo-adapted Charlson Comorbid Index	1.7	2.7	1.8	2.9	1.6	2.7
Deyo-adapted CCI=0	248	51.5%	87	52.4%	180	54.9%
Deyo-adapted CCI=1 or 2	118	24.5%	39	23.5%	84	25.6%
Deyo-adapted CCI≥3	116	24.1%	40	24.1%	64	19.5%
AIDS	79	16.4%	29	17.5%	45	13.7%
Opportunistic Infection	114	23.7%	45	27.1%	66	20.1%

Table 5.12 Baseline Characteristics at Different Adherence among Patient on Boosted PIs

	Patients at initial coverage ratio of complete regimen ≥ 95% (N=1291)		Patients at initial coverage ratio of complete regimen 75–<95% (N=327)		Patients at initial coverage ratio of complete regimen <75% (N=679)	
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%
Age	47.6	10.6	47.9	10.3	48.5	10.3
18-35 years old	182	14.1%	44	13.5%	80	11.9%
36-50 years old	586	45.4%	138	42.2%	272	40.4%
51-65 years old	476	36.9%	136	41.6%	298	44.3%
>65 years old	47	3.6%	9	2.8%	23	3.4%
Male	1251	96.9%	316	96.6%	646	96.0%
Race/Ethnicity White	402	31.1%	90	27.5%	155	23.0%
African-American	671	52.0%	181	55.4%	422	62.7%
Hispanic	81	6.3%	19	5.8%	36	5.3%
Others	19	1.5%	7	2.1%	7	1.0%
Unknown	118	9.1%	30	9.2%	53	7.9%
SES 1st Quartile	275	21.3%	65	19.9%	186	27.6%
2nd Quartile	281	21.8%	76	23.2%	146	21.7%
3rd Quartile	277	21.5%	67	20.5%	140	20.8%
4th Quartile	291	22.5%	73	22.3%	130	19.3%
Unknown	167	12.9%	46	14.1%	71	10.5%
Viral Load (1000 copies/mm3)	266.3	727.9	194.4	432.8	163.5	339.9
<10,000	210	16.3%	62	19.0%	127	18.9%
10,000–<50,000	286	22.2%	71	21.7%	174	25.9%
50,000–<100,000	199	15.4%	51	15.6%	104	15.5%
100,000–<500,000	409	31.7%	107	32.7%	210	31.2%
≥500,000	187	14.5%	36	11.0%	58	8.6%

Table 5.12 Continued

	Patients at initial coverage ratio of complete regimen ≥ 95% (N=1291)		Patients at initial coverage ratio of complete regimen 75–<95% (N=327)		Patients at initial coverage ratio of complete regimen <75% (N=679)	
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%
CD4 Counts (cells/mm3)	233.1	216.0	224.6	187.8	254.9	226.4
<200	471	36.5%	128	39.1%	256	38.0%
200–499	351	27.2%	94	28.7%	169	25.1%
≥500	89	6.9%	23	7.0%	51	7.6%
Unknown	380	29.4%	82	25.1%	197	29.3%
All agents in a single pill	0	0.0%	0	0.0%	0	0.0%
Deyo-adapted Charlson Comorbid Index	2.3	3.1	2.4	3.2	2.4	3.3
Deyo-adapted CCI=0	547	42.4%	134	41.0%	293	43.5%
Deyo-adapted CCI=1 or 2	347	26.9%	93	28.4%	170	25.3%
Deyo-adapted CCI≥3	397	30.8%	100	30.6%	210	31.2%
AIDS	252	19.5%	67	20.5%	129	19.2%
Opportunistic Infection	389	30.1%	89	27.2%	184	27.3%

Table 5.13 Baseline Characteristics at Different Adherence among Patient on NNRTIs

	Patients at initial coverage ratio of complete regimen ≥ 95% (N=3727)		Patients at initial coverage ratio of complete regimen 75–<95% (N=912)		Patients at initial coverage ratio of complete regimen <75% (N=1735)	
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%
Age	47.3	11.2	47.0	11.2	47.4	10.6
18–35 years old	595	16.0%	156	17.1%	257	14.8%
36–50 years old	1632	43.8%	404	44.3%	797	45.9%
51–65 years old	1328	35.6%	309	33.9%	613	35.3%
>65 years old	172	4.6%	43	4.7%	68	3.9%
Male	3605	96.8%	877	96.3%	1669	96.2%
Race/Ethnicity White	157	38.6%	27	28.1%	25	19.2%
African-American	184	45.2%	53	55.2%	90	69.2%
Hispanic	26	6.4%	9	9.4%	10	7.7%
Others	10	2.5%	0	0.0%	1	0.8%
Unknown	30	7.4%	7	7.3%	4	3.1%
SES 1st Quartile	783	21.0%	179	19.6%	450	25.9%
2nd Quartile	803	21.5%	232	25.4%	354	20.4%
3rd Quartile	865	23.2%	210	23.0%	356	20.5%
4th Quartile	888	23.8%	186	20.4%	366	21.1%
Unknown	388	10.4%	105	11.5%	209	12.0%
Viral Load (1000 copies/mm3)	172.9	520.4	188.7	656.7	115.1	216.5
<10,000	684	18.4%	202	22.1%	398	22.9%
10,000–<50,000	979	26.3%	226	24.8%	519	29.9%
50,000–<100,000	693	18.6%	153	16.8%	305	17.6%
100,000–<500,000	1045	28.0%	264	28.9%	414	23.9%
≥500,000	326	8.7%	67	7.3%	99	5.7%

Table 5.13 Continued

	Patients at initial coverage ratio of complete regimen ≥ 95% (N=3727)		Patients at initial coverage ratio of complete regimen 75–<95% (N=912)		Patients at initial coverage ratio of complete regimen <75% (N=1735)	
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%
CD4 Counts (cells/mm3)	268.9	207.7	277.4	196.9	275.8	202.9
<200	1122	30.1%	265	29.1%	512	29.5%
200–499	1353	36.3%	353	38.7%	662	38.2%
≥500	326	8.7%	89	9.8%	165	9.5%
Unknown	926	24.8%	205	22.5%	396	22.8%
All agents in a single pill	1956	52.5%	464	50.9%	748	43.1%
Deyo-adapted Charlson Comorbid Index	2.1	2.9	2.1	2.9	2.2	3.0
Deyo-adapted CCI=0	1646	44.2%	406	44.5%	761	43.9%
Deyo-adapted CCI=1 or 2	1043	28.0%	246	27.0%	465	26.8%
Deyo-adapted CCI≥3	1038	27.9%	260	28.5%	509	29.3%
AIDS	629	16.9%	156	17.1%	315	18.2%
Opportunistic Infection	960	25.8%	216	23.7%	416	24.0%

Table 5.14 Baseline Characteristics at Different Adherence among Patient on INSTIs

	Patients at initial coverage ratio of complete regimen ≥ 95% (N=407)		Patients at initial coverage ratio of complete regimen 75–<95% (N=96)		Patients at initial coverage ratio of complete regimen <75% (N=130)	
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%
Age	47.5	13.4	46.3	12.6	46.0	13.0
18–35 years old	97	23.8%	23	24.0%	32	24.6%
36–50 years old	131	32.2%	34	35.4%	50	38.5%
51–65 years old	146	35.9%	34	35.4%	42	32.3%
>65 years old	33	8.1%	5	5.2%	6	4.6%
Male	388	95.3%	89	92.7%	123	94.6%
Race/Ethnicity White	157	38.6%	27	28.1%	25	19.2%
African-American	184	45.2%	53	55.2%	90	69.2%
Hispanic	26	6.4%	9	9.4%	10	7.7%
Others	10	2.5%	0	0.0%	1	0.8%
Unknown	30	7.4%	7	7.3%	4	3.1%
SES 1st Quartile	71	17.4%	20	20.8%	33	25.4%
2nd Quartile	102	25.1%	21	21.9%	32	24.6%
3rd Quartile	101	24.8%	28	29.2%	34	26.2%
4th Quartile	102	25.1%	20	20.8%	23	17.7%
Unknown	31	7.6%	7	7.3%	8	6.2%
Viral Load (1000 copies/mm3)	271.6	959.8	111.6	213.7	157.0	467.5
<10,000	83	20.4%	33	34.4%	23	17.7%
10,000–<50,000	130	31.9%	21	21.9%	44	33.8%
50,000–<100,000	62	15.2%	16	16.7%	18	13.8%
100,000–<500,000	93	22.9%	22	22.9%	39	30.0%
≥500,000	39	9.6%	4	4.2%	6	4.6%

Table 5.14 Continued

	Patients at initial coverage ratio of complete regimen ≥ 95% (N=407)		Patients at initial coverage ratio of complete regimen 75–<95% (N=96)		Patients at initial coverage ratio of complete regimen <75% (N=130)	
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%
CD4 Counts (cells/mm3)	369.5	254.4	375.5	252.3	376.0	281.8
<200	86	21.1%	18	18.8%	28	21.5%
200-499	135	33.2%	40	41.7%	50	38.5%
≥500	80	19.7%	21	21.9%	27	20.8%
Unknown	106	26.0%	17	17.7%	25	19.2%
All agents in a single pill	169	41.5%	31	32.3%	59	45.4%
Deyo-adapted Charlson Comorbid Index	2.5	3.2	2.5	3.2	2.8	3.5
Deyo-adapted CCI=0	154	37.8%	39	40.6%	45	34.6%
Deyo-adapted CCI=1 or 2	118	29.0%	24	25.0%	41	31.5%
Deyo-adapted CCI≥3	135	33.2%	33	34.4%	44	33.9%
AIDS	72	17.7%	15	15.6%	26	20.0%
Opportunistic Infection	77	18.9%	16	16.7%	26	20.0%

Table 5.15 Baseline Characteristics and Initial Adherence Comparison between Patients with and without Viral Outcomes within 30-60 Days

	Patients with viral outcome (N=4,319)		Patients without viral outcome (N=5,955)		P-value
	Mean/N	SD/%	Mean/N	SD/%	
Demographics					
Age	47.7	10.8	47.1	10.9	0.0015
18–35 years old	612	14.2%	959	16.1%	0.0069
36–50 years old	1913	44.3%	2692	45.2%	
51–65 years old	1601	37.1%	2071	34.8%	
>65 years old	193	4.5%	233	3.9%	
Male	4176	96.7%	5745	96.5%	0.4735
Race/Ethnicity					
White	1297	30.0%	1675	28.1%	0.038
African-American	2323	53.8%	3361	56.4%	
Hispanic	297	6.9%	367	6.2%	
Others	57	1.3%	62	1.0%	
Unknown	345	8.0%	490	8.2%	
Social Economic Status					
1st Quartile	916	21.2%	1374	23.1%	0.199
2nd Quartile	946	21.9%	1318	22.1%	
3rd Quartile	982	22.7%	1294	21.7%	
4th Quartile	977	22.6%	1301	21.8%	
Unknown	498	11.5%	668	11.2%	
Baseline Labs					
Viral Load (1000 copies/mm3)	204.6	600.6	156	451.8	<0.0001
<10,000	740	17.1%	1292	21.7%	<0.0001
10,000–<50,000	1096	25.4%	1587	26.6%	
50,000–<100,000	757	17.5%	1034	17.4%	
100,000–<500,000	1273	29.5%	1576	26.5%	
≥500,000	453	10.5%	466	7.8%	
CD4 Counts (cells/mm3)	260.4	210.7	271.4	213.6	0.0252
<200	1423	32.9%	1821	30.6%	0.056
200–499	1461	33.8%	2034	34.2%	
≥500	386	8.9%	568	9.5%	
Unknown	1049	24.3%	1532	25.7%	

Table 5.16 Binary Adherence Effect Estimates on Viral Suppression

Initiated Regimen	Adherence	Pooled Estimate Based on Five Imputed Datasets			
		Crude Odds Ratio		Weighted Odds Ratio	
		Estimate	95% Confidence Interval	Estimate	95% Confidence Interval
Unboosted PI	<95% vs. ≥95%	0.39	0.22-0.70	0.33	0.18-0.63
	<90% vs. ≥90%	0.32	0.17-0.61	0.27	0.14-0.54
	<85% vs. ≥85%	0.22	0.07-0.67	0.18	0.05-0.62
	<80% vs. ≥80%	0.21	0.07-0.63	0.18	0.06-0.55
	<75% vs. ≥75%	0.21	0.08-0.56	0.18	0.06-0.51
Boosted PI	<95% vs. ≥95%	0.42	0.28-0.63	0.40	0.26-0.62
	<90% vs. ≥90%	0.38	0.23-0.62	0.36	0.22-0.60
	<85% vs. ≥85%	0.39	0.25-0.61	0.38	0.24-0.60
	<80% vs. ≥80%	0.34	0.20-0.57	0.34	0.20-0.58
	<75% vs. ≥75%	0.32	0.17-0.58	0.31	0.17-0.58
NNRTI	<95% vs. ≥95%	0.55	0.45-0.68	0.50	0.40-0.62
	<90% vs. ≥90%	0.52	0.40-0.68	0.47	0.36-0.63
	<85% vs. ≥85%	0.46	0.33-0.63	0.41	0.29-0.58
	<80% vs. ≥80%	0.45	0.32-0.63	0.40	0.27-0.58
	<75% vs. ≥75%	0.39	0.27-0.57	0.35	0.23-0.54
INSTI	<95% vs. ≥95%	0.48	0.34-0.68	0.44	0.31-0.62
	<90% vs. ≥90%	0.41	0.28-0.58	0.37	0.25-0.54
	<85% vs. ≥85%	0.32	0.21-0.50	0.31	0.20-0.50
	<80% vs. ≥80%	0.30	0.19-0.48	0.30	0.18-0.50
	<75% vs. ≥75%	0.27	0.16-0.46	0.26	0.15-0.47

Table 5.17 Multilevel Adherence Effect Estimates on Viral Suppression Based on Imputed Data

Initiated Regimen	Adherence	Pooled Estimate Based on Five Imputed Datasets			
		Crude Odds Ratio		Weighted Odds Ratio	
		Estimate	95% Confidence Interval	Estimate	95% Confidence Interval
Unboosted PI	75-<95% vs. ≥95%	0.79	0.44-1.42	0.63	0.32-1.21
	<75% vs. ≥95%	0.16	0.05-0.53	0.13	0.03-0.50
Boosted PI	75-<95% vs. ≥95%	0.65	0.41-1.04	0.64	0.41-1.01
	<75% vs. ≥95%	0.29	0.16-0.52	0.28	0.16-0.51
NNRTI	75-<95% vs. ≥95%	0.94	0.73-1.20	0.87	0.68-1.10
	<75% vs. ≥95%	0.38	0.26-0.56	0.34	0.22-0.52
INSTI	75-<95% vs. ≥95%	0.92	0.55-1.52	0.89	0.52-1.52
	<75% vs. ≥95%	0.26	0.15-0.45	0.25	0.14-0.45

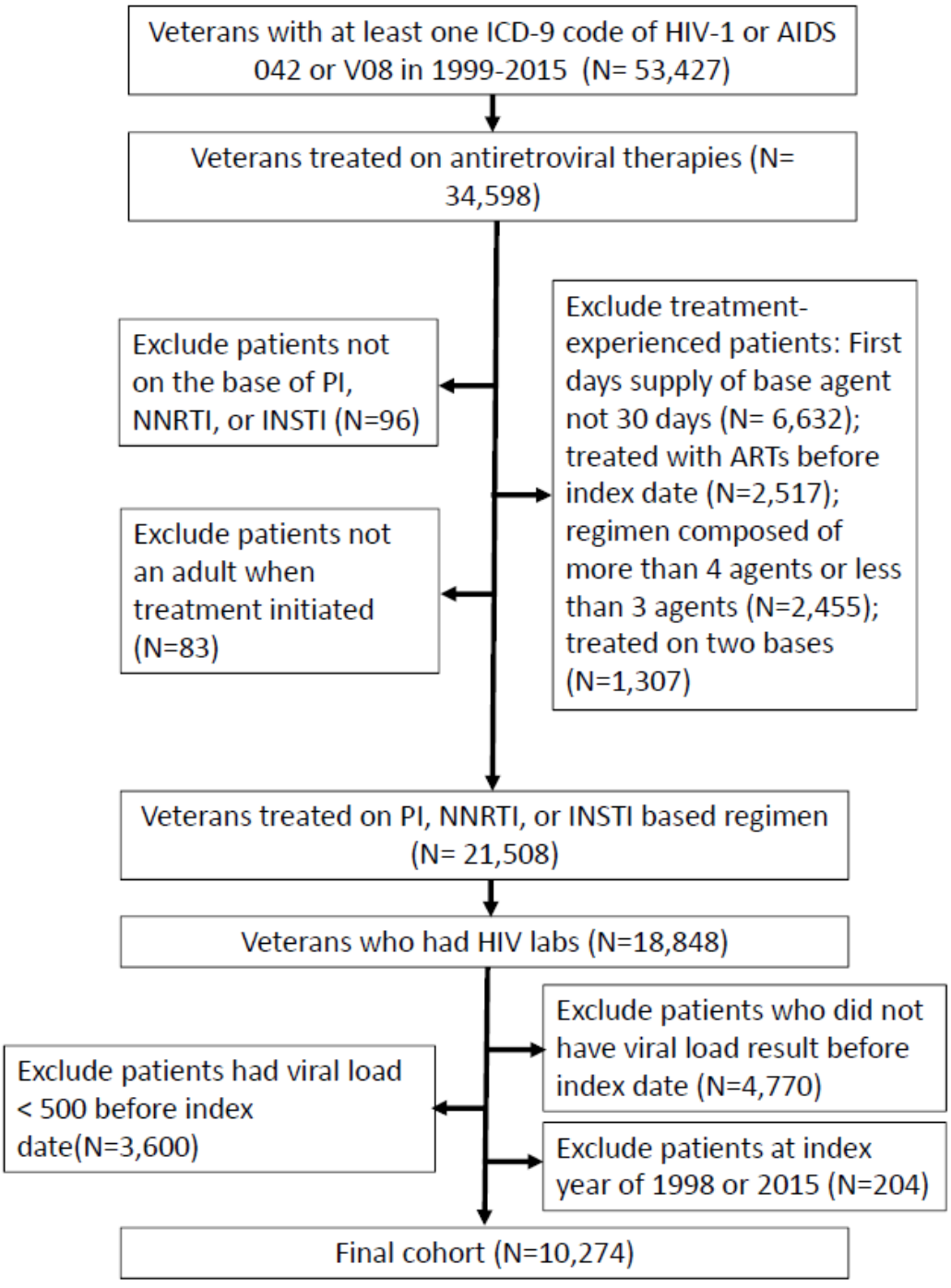


Figure 5.1 Cohort Selection Flow Chart

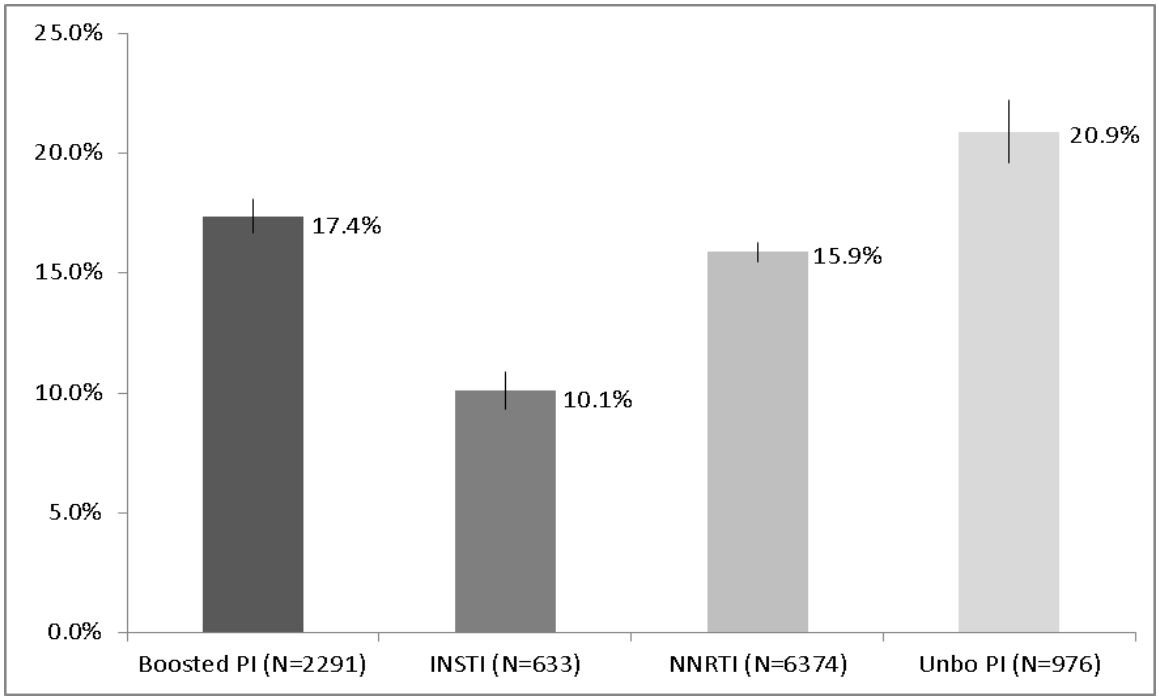


Figure 5.2 Discontinuation (No Second Fill in 60 Days) Rate across Initiated Regimens

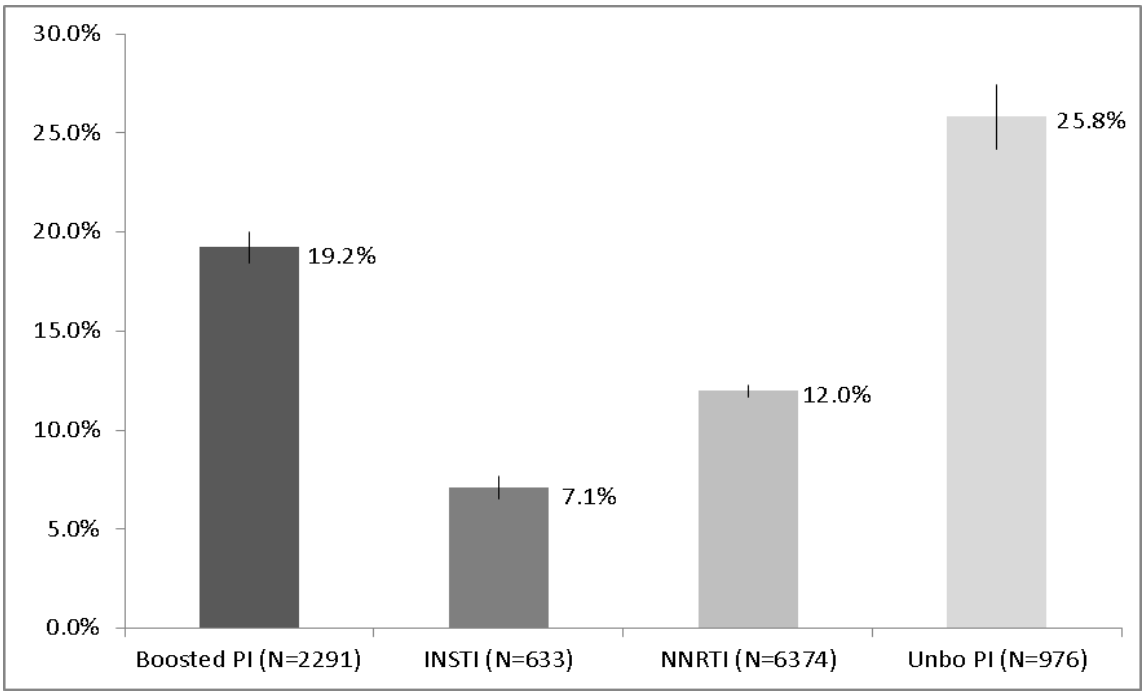


Figure 5.3 Proportion of Patients Switching Regimen Category

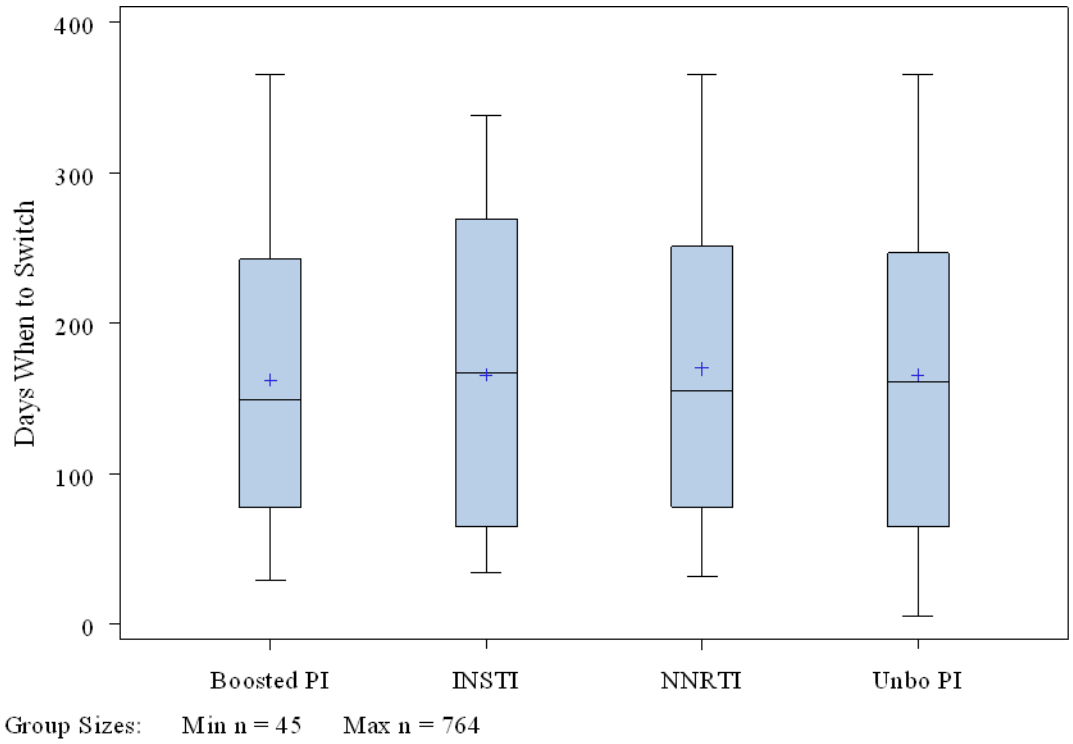


Figure 5.4 Days Switch among Patients Who Switched Initiated Regimen

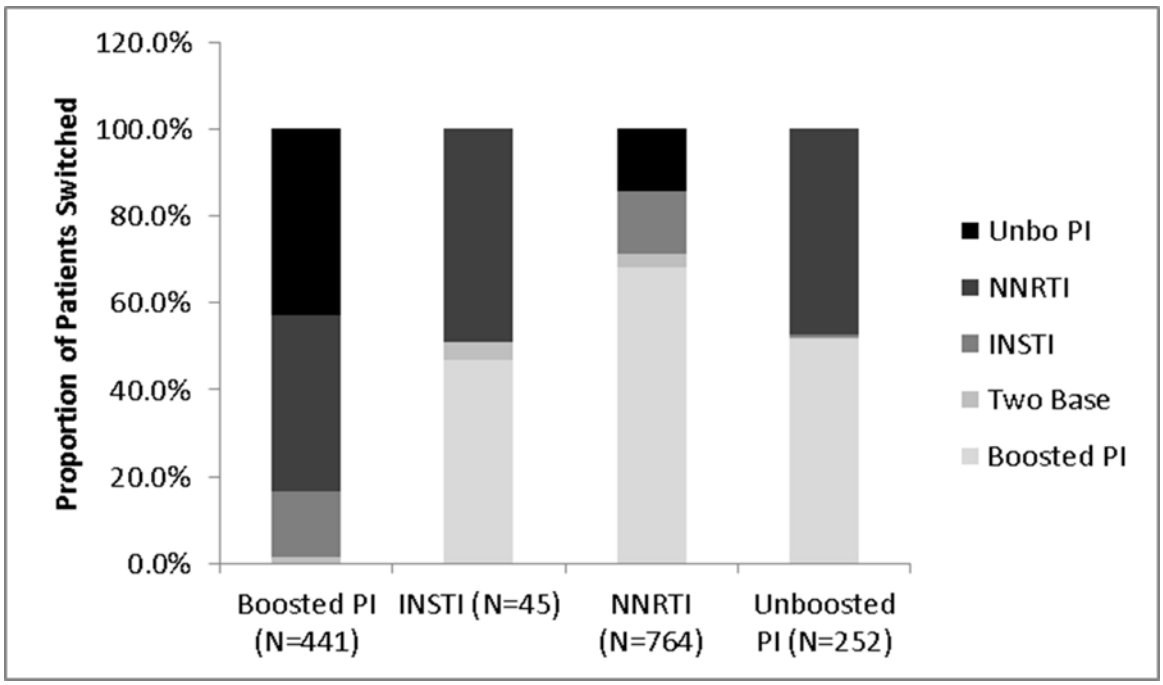


Figure 5.5 Switching Pattern for Patients Switching Regimen Category

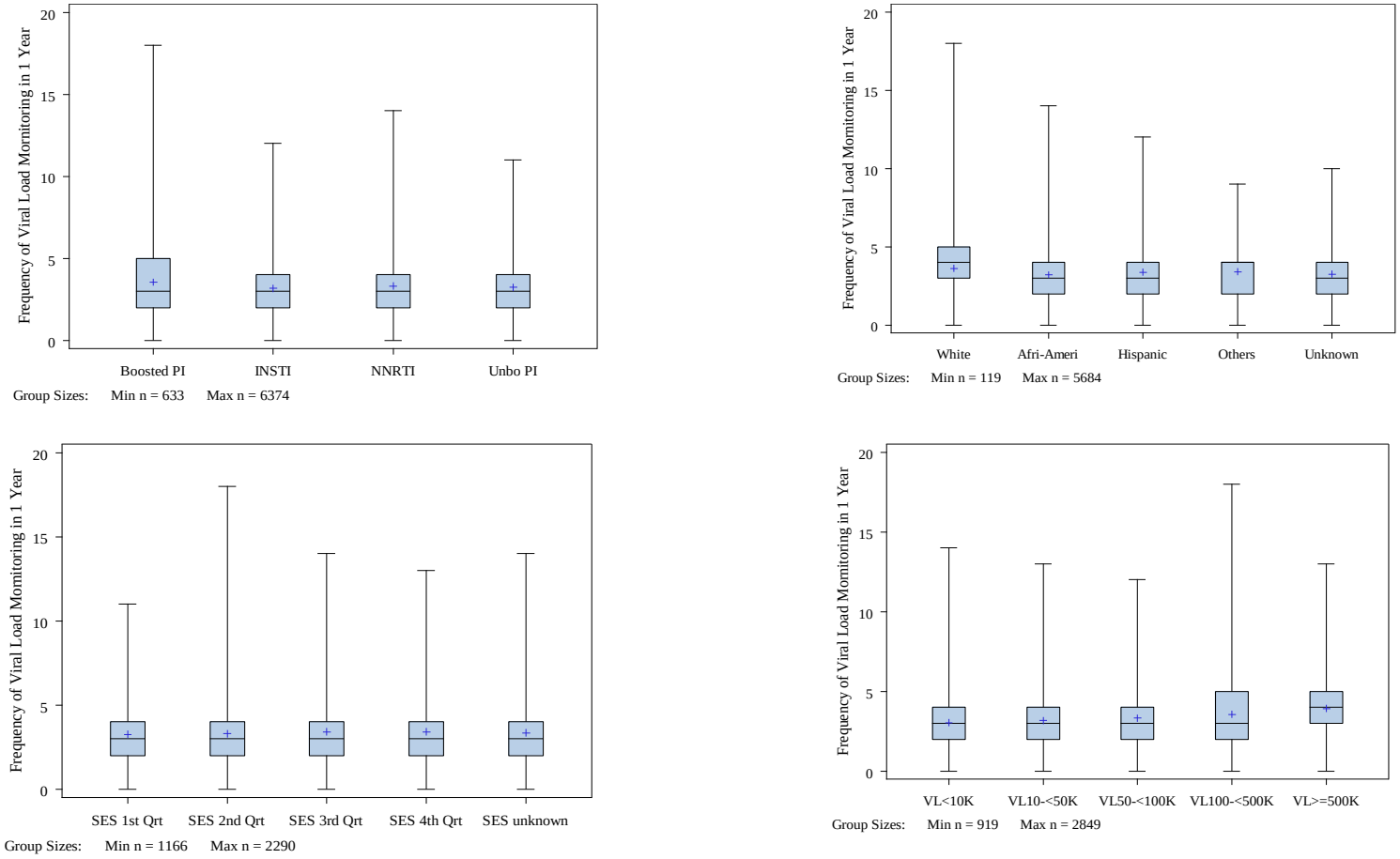
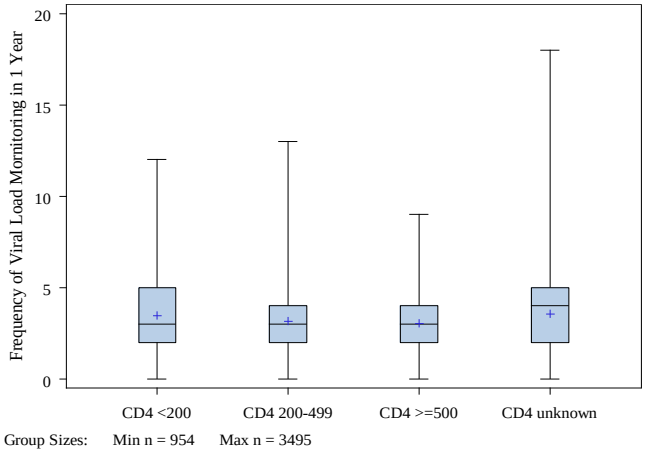
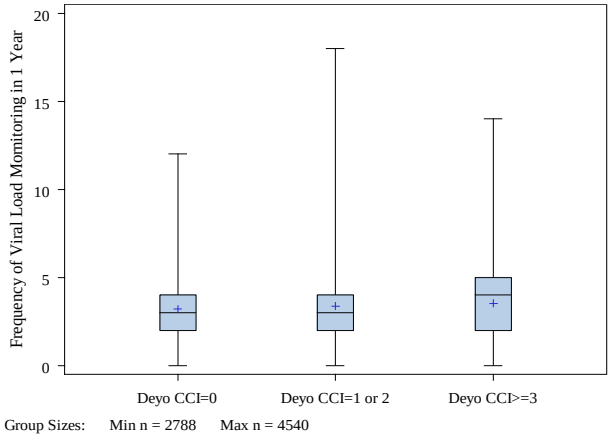


Figure 5.6 Viral Load Monitoring Frequency in One Year since Index Date





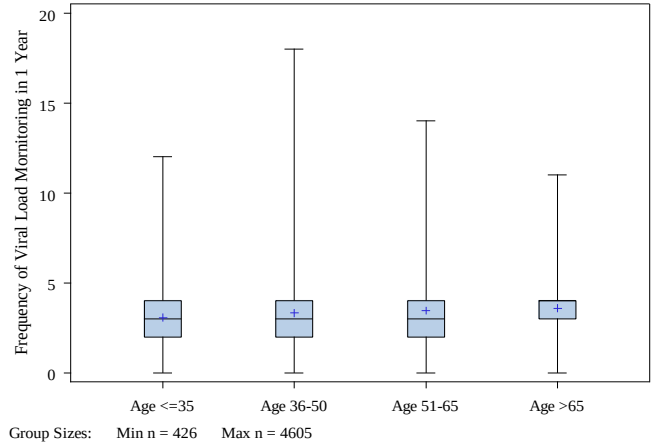


Figure 5.6 Continued

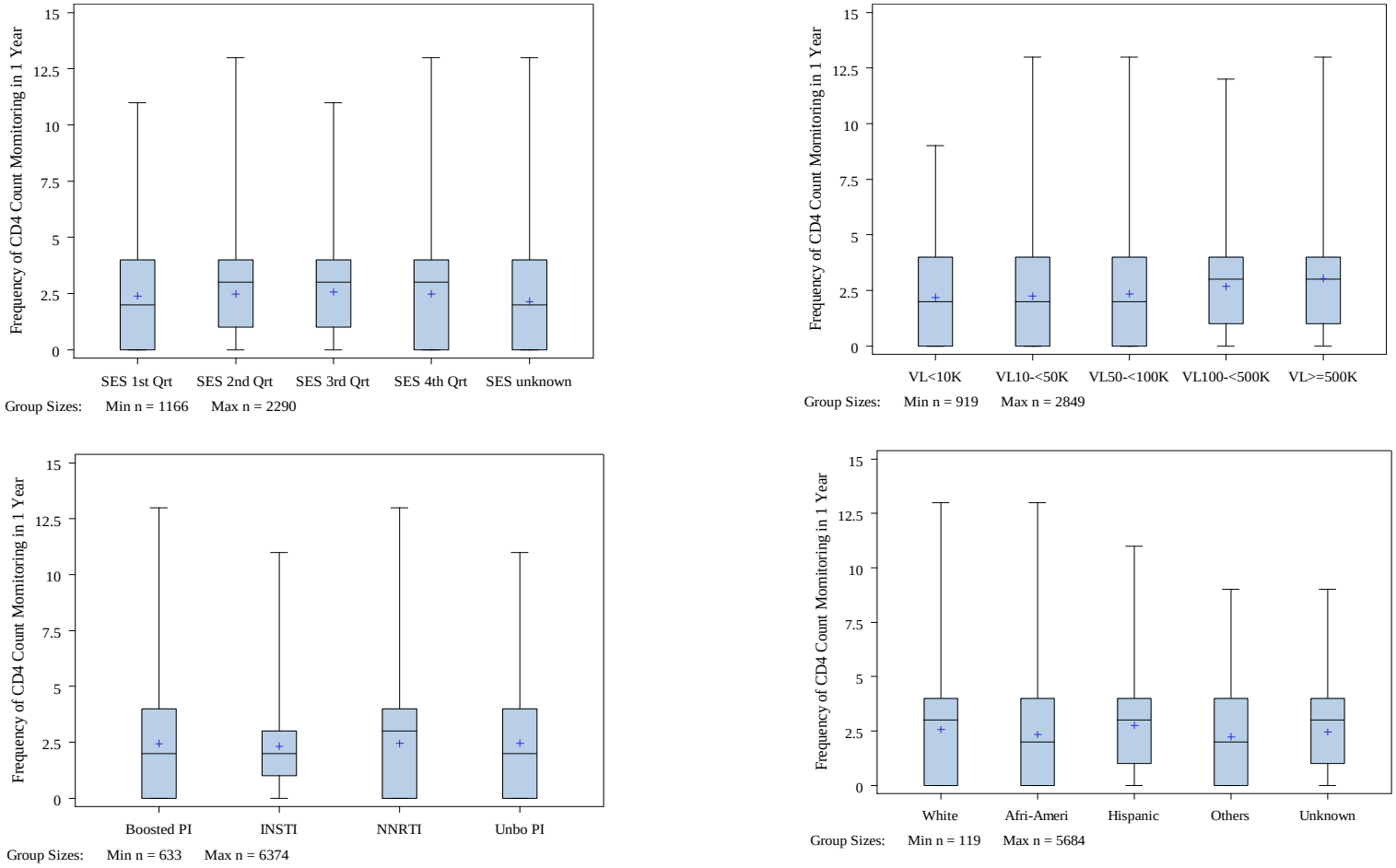
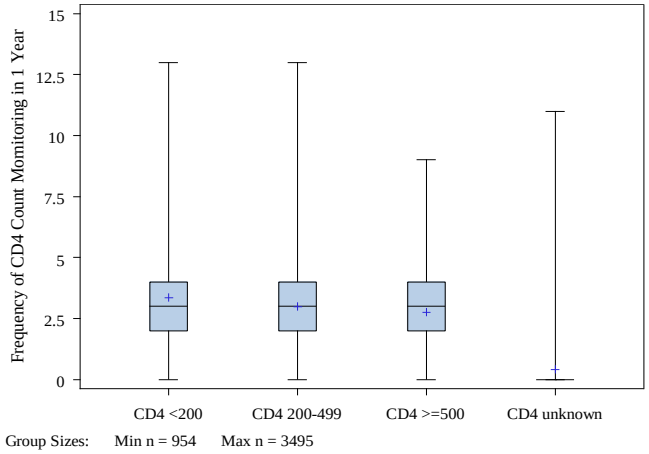
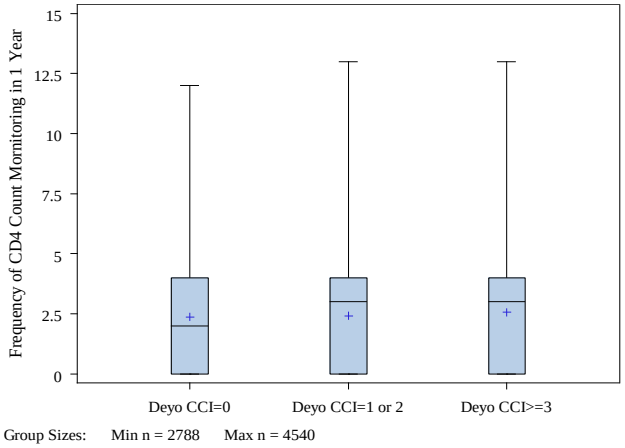


Figure 5.7 CD4 Count Test Frequency in One Year since Index Da





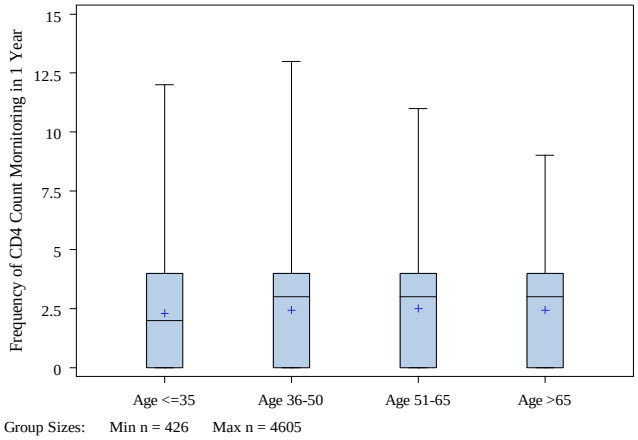


Figure 5.7 Continued

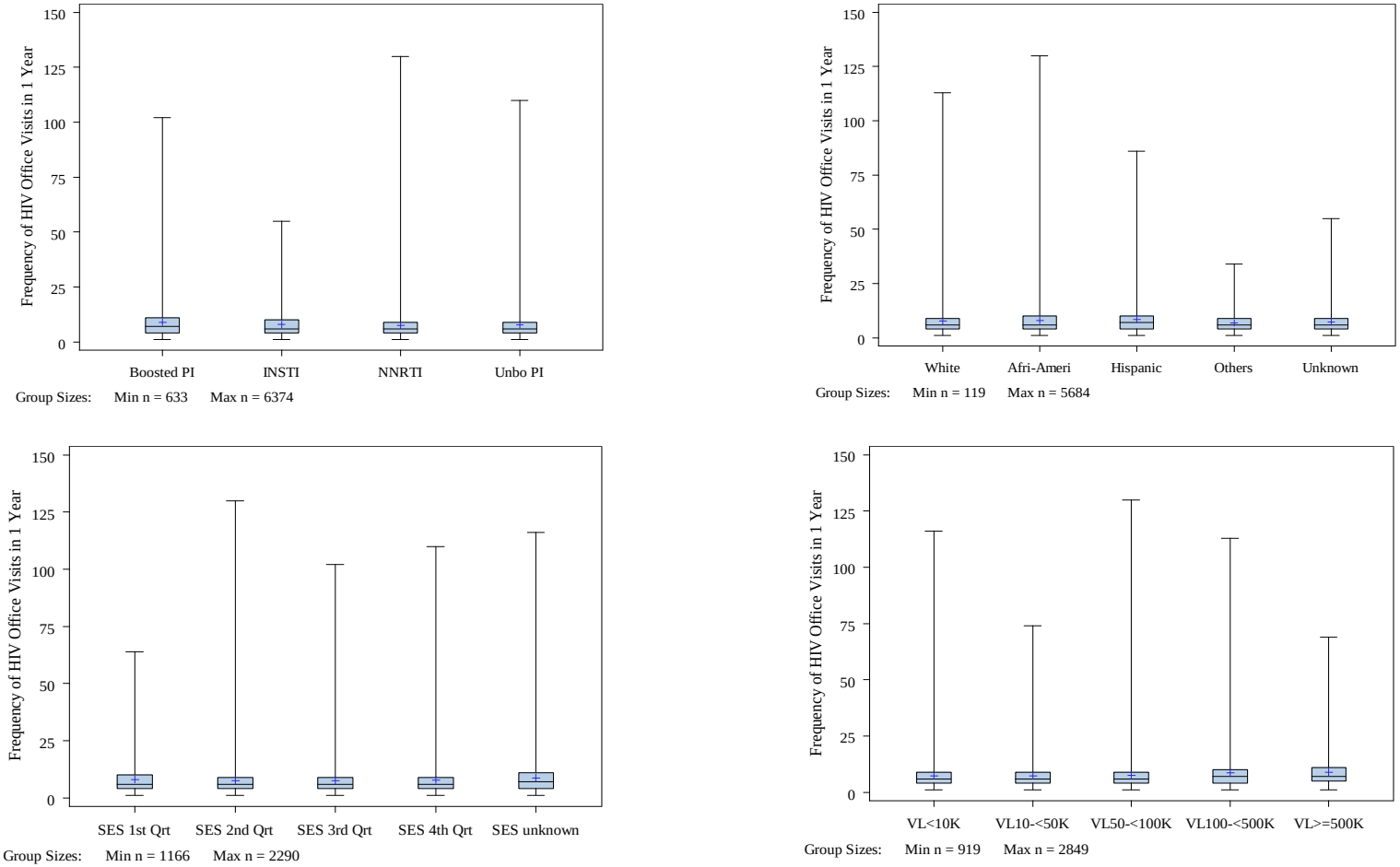
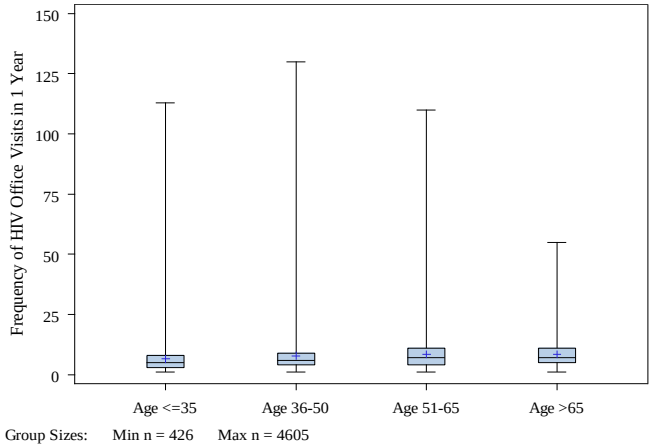
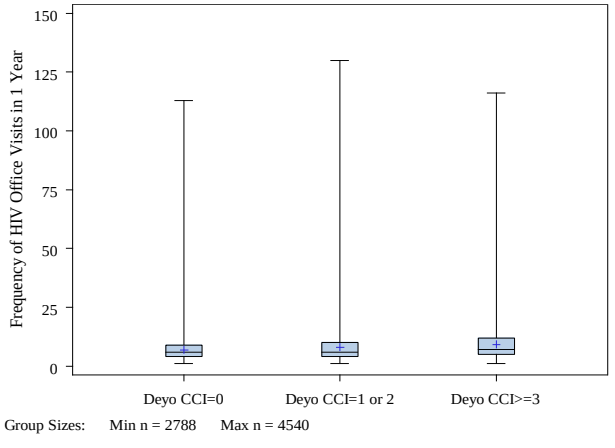


Figure 5.8 HIV Office Visit Frequency in One Year since Index Date





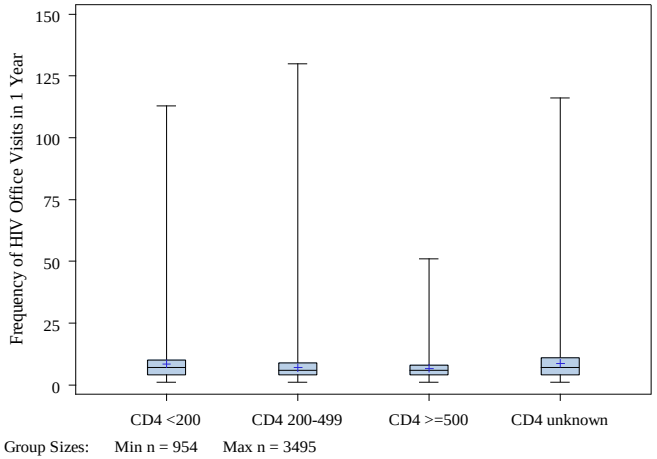


Figure 5.8 Continued

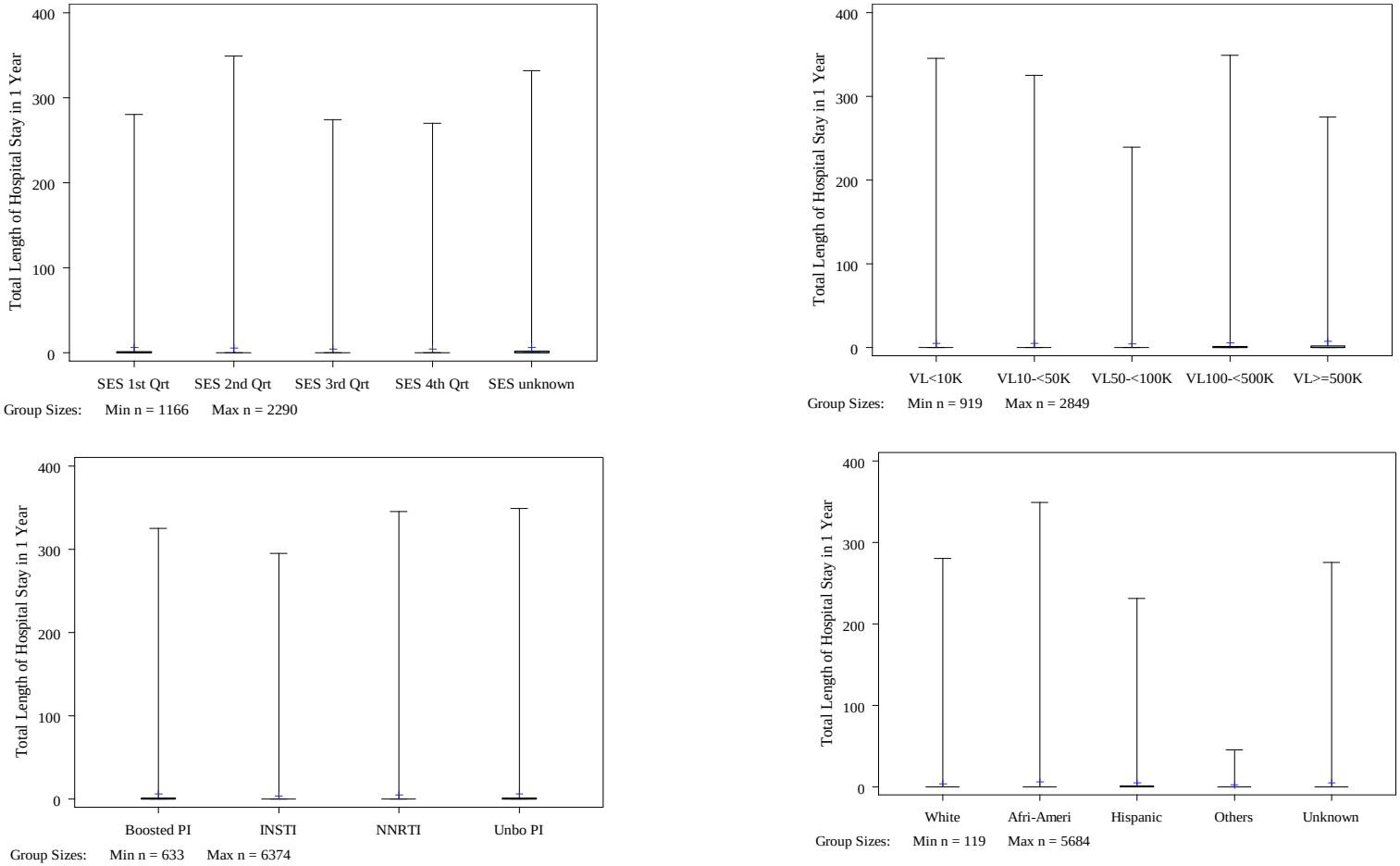
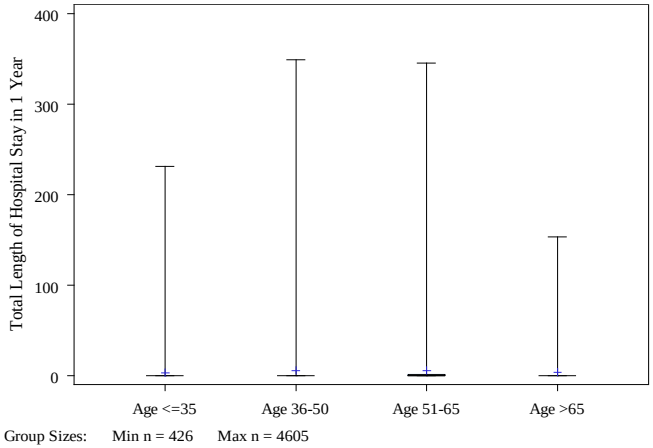
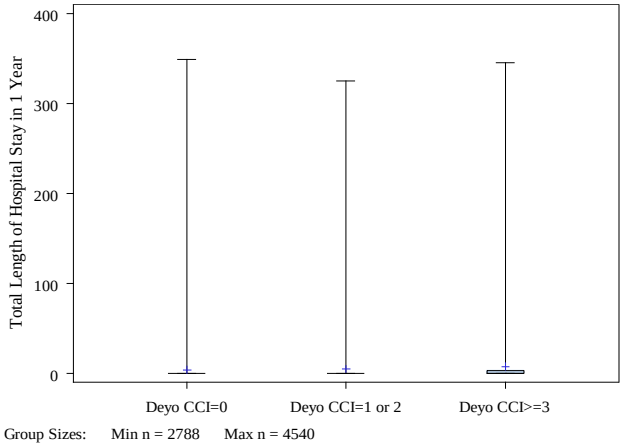


Figure 5.9 Length of Stay in One Year since Index Date among All Patients





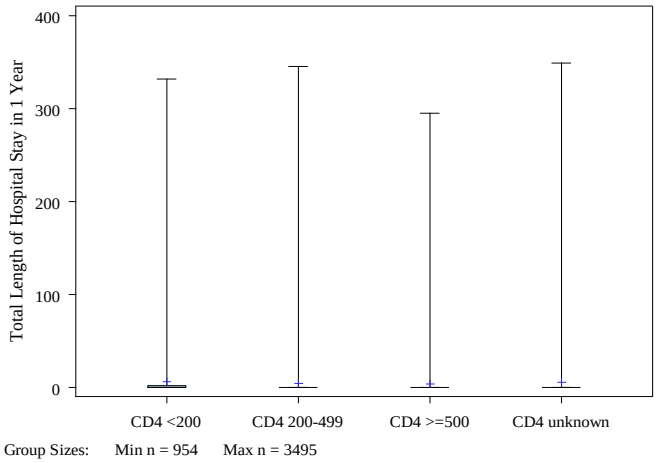


Figure 5.9 Continued

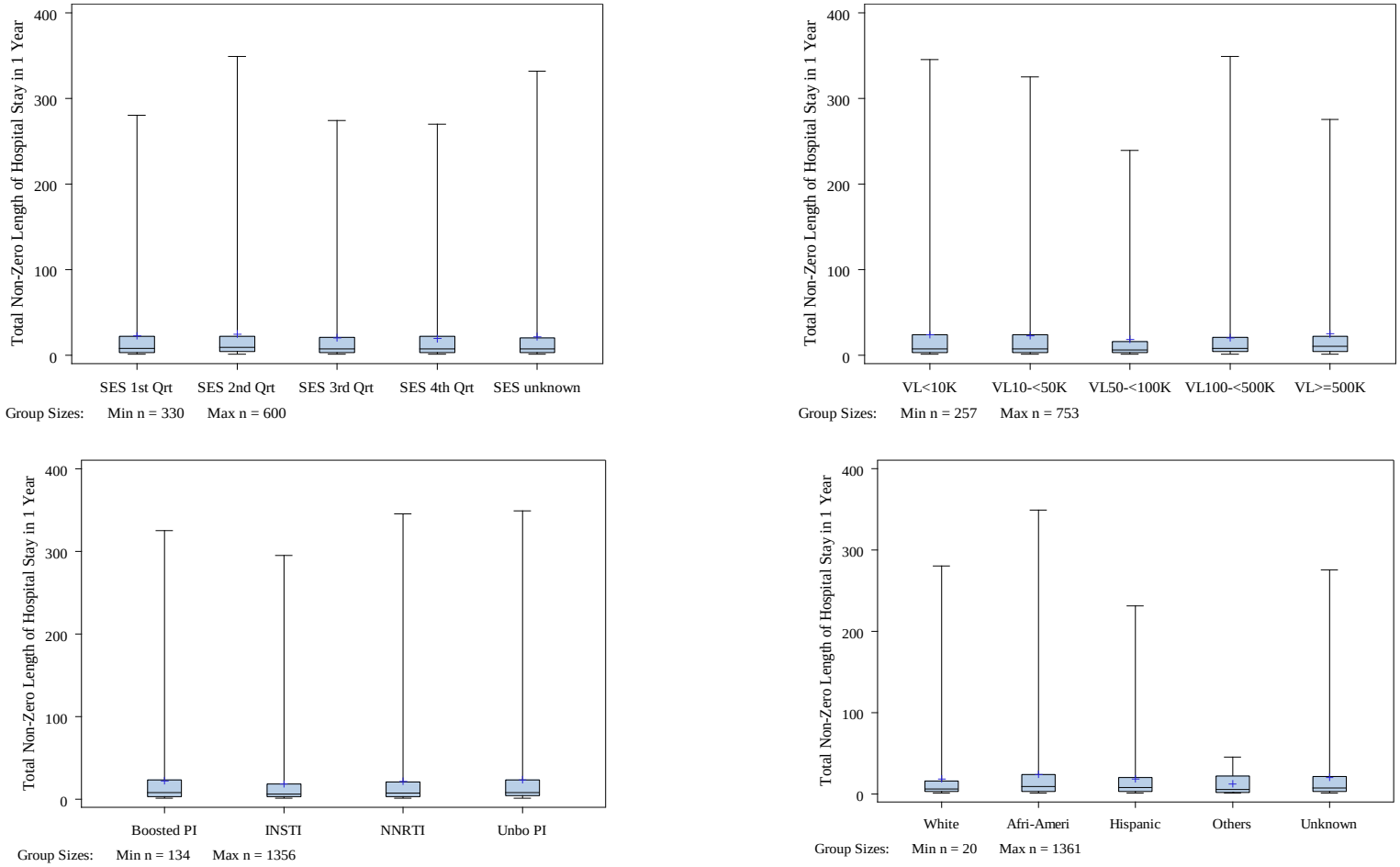
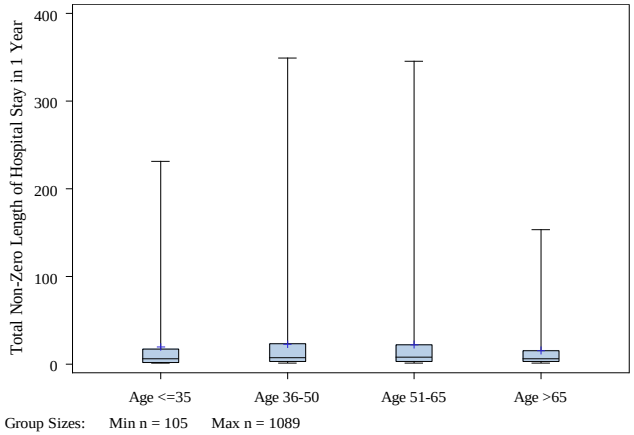
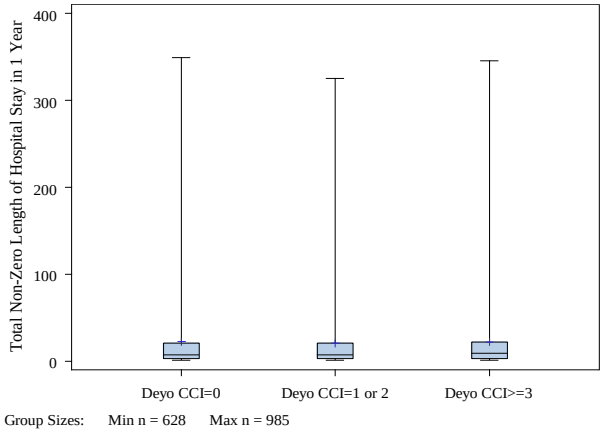


Figure 5.10 Length of Stay in One Year since Index Date among Hospitalized Patients





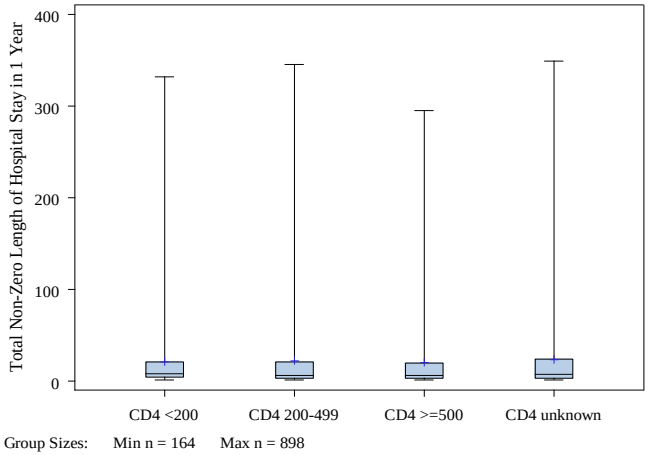


Figure 5.10 Continued

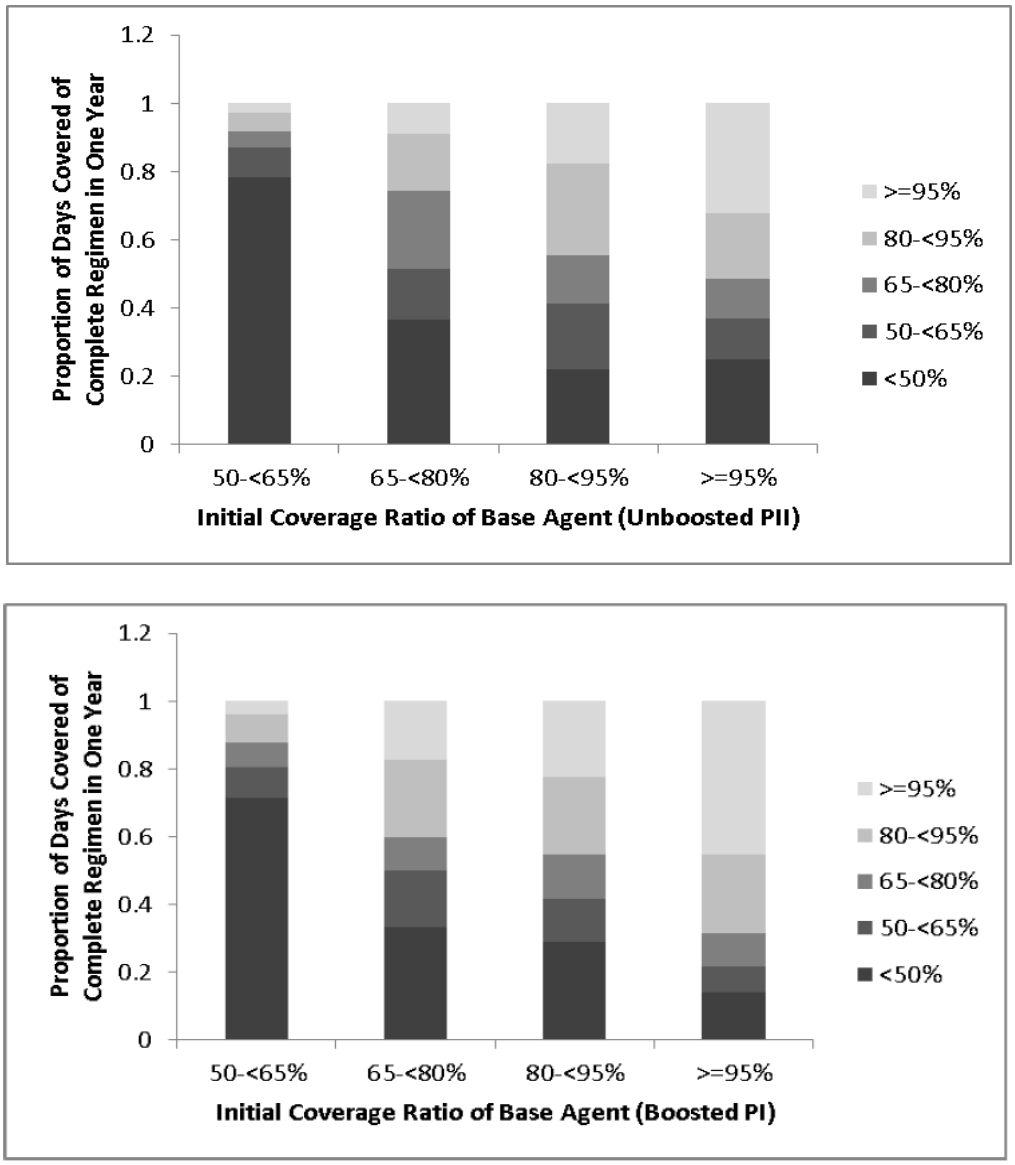


Figure 5.11 Adherence Change Pattern by Initiated Regimen

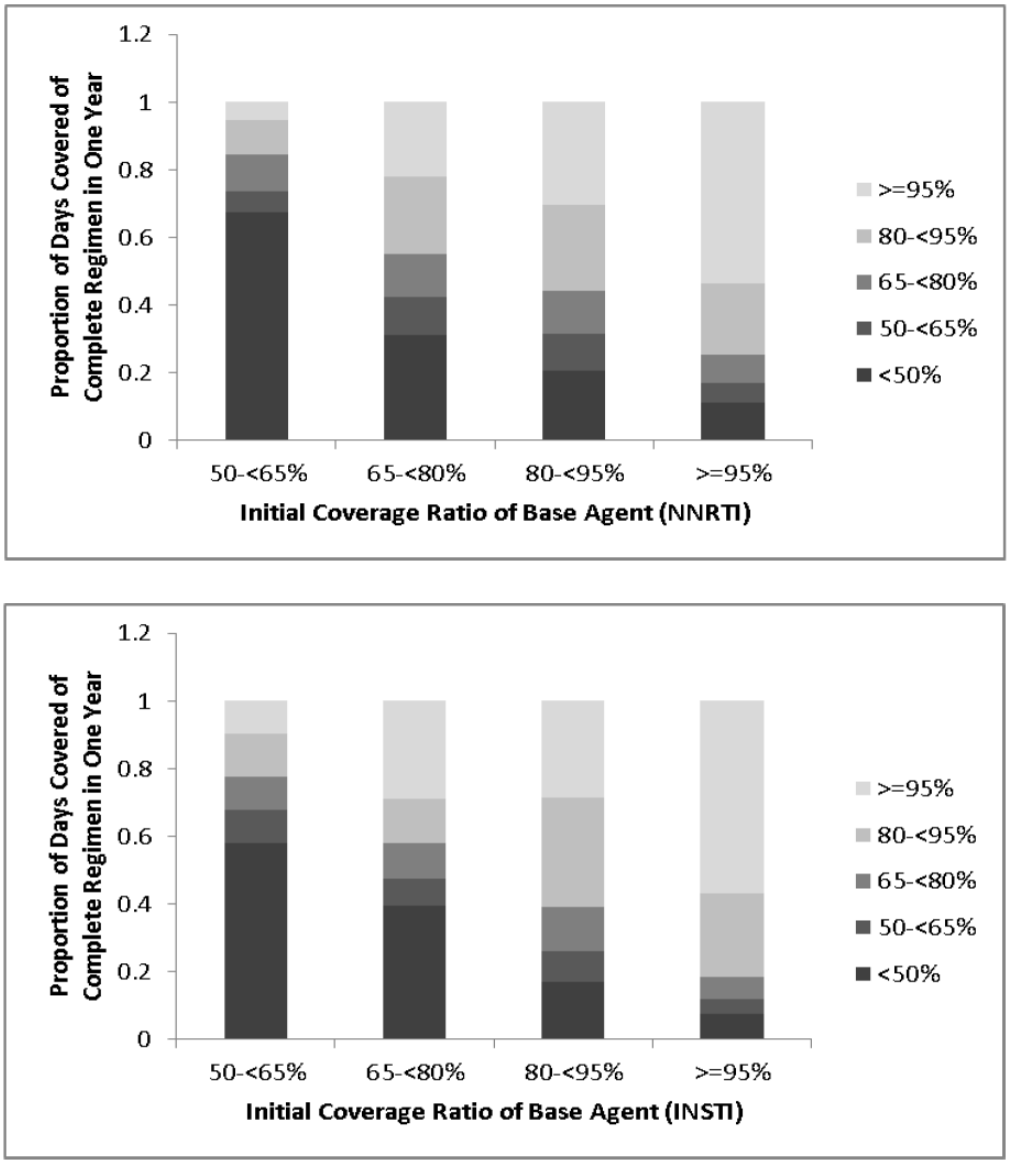


Figure 5.11 Continued

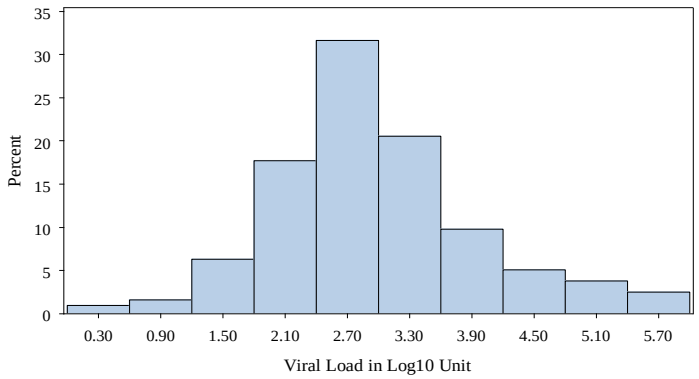
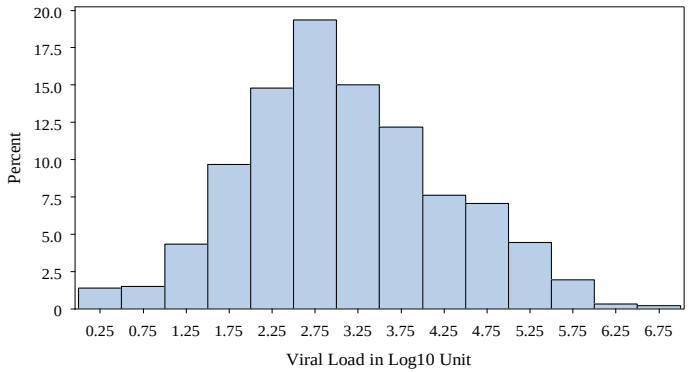
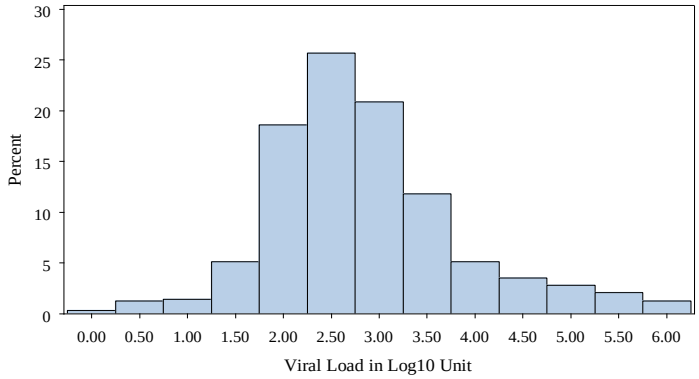
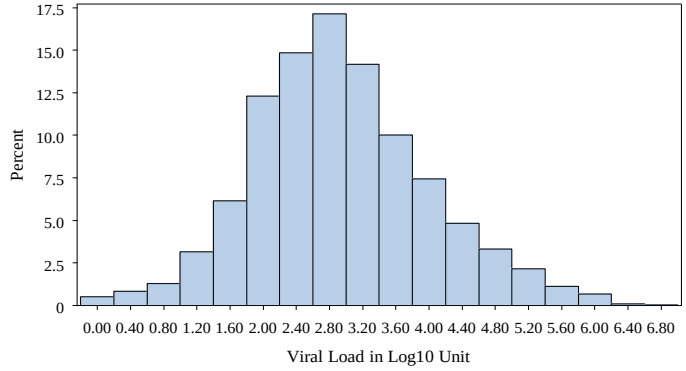
Regimen	Data Distribution (Complete Cases)	Data Distribution (One of Five Imputed Datasets)
Unboosted PI		
Boosted PI		

Figure 5.12 Distribution of Viral Load in Log10 before and after Imputation

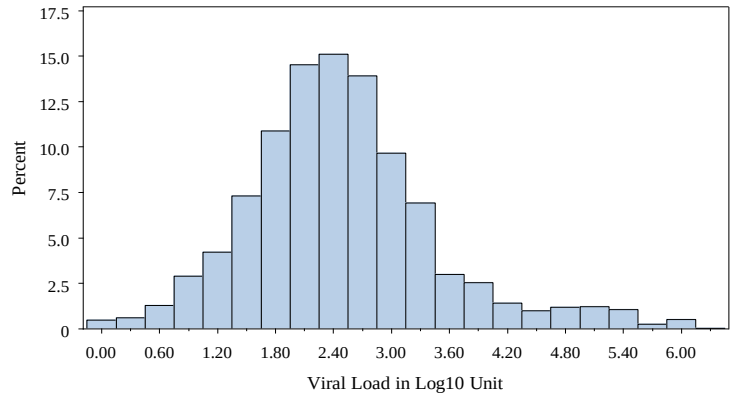
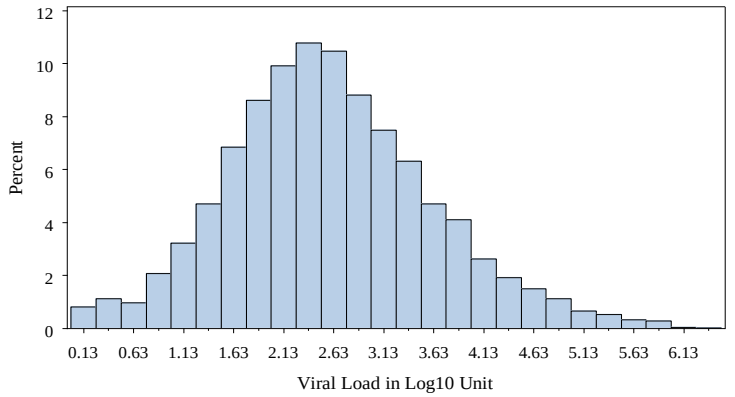
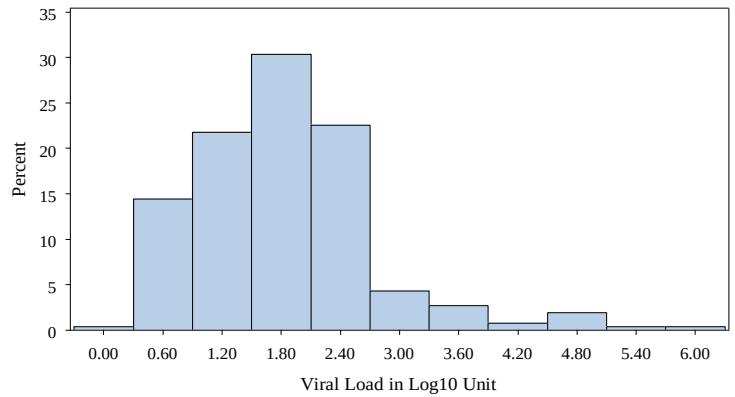
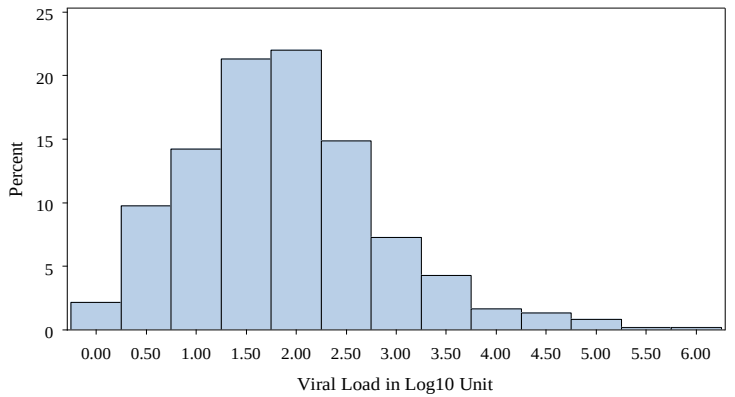
NNRTI		
INSTI		

Figure 5.12 Continued

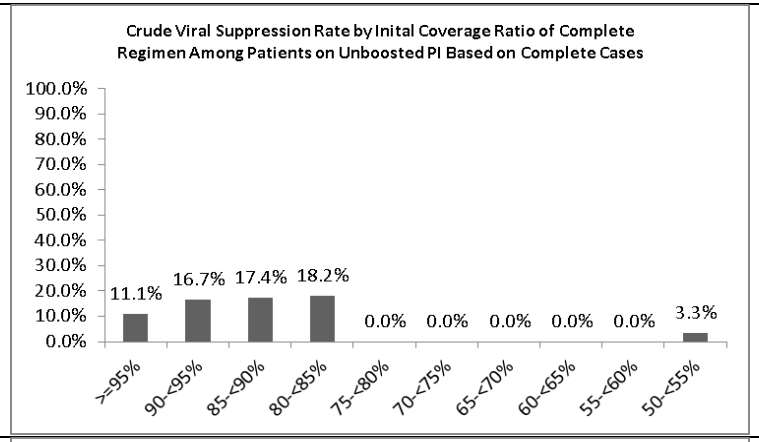
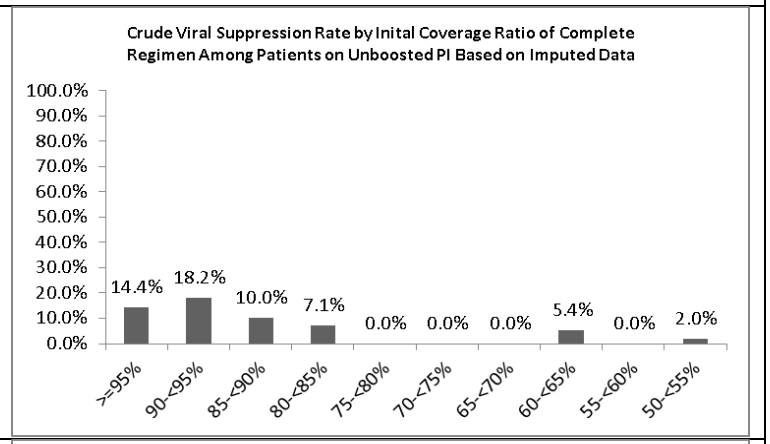
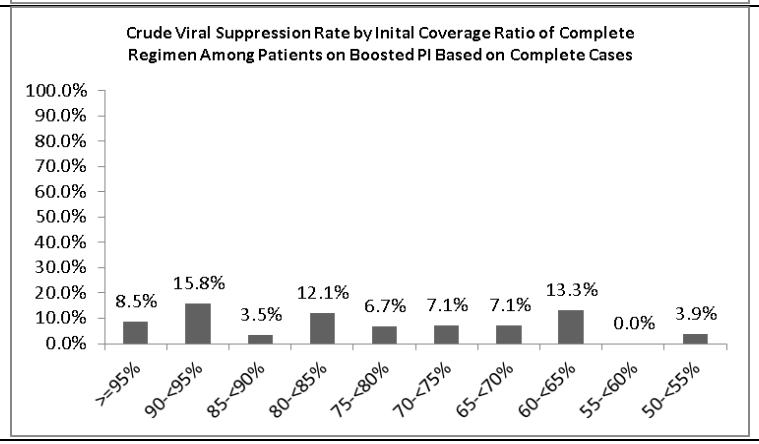
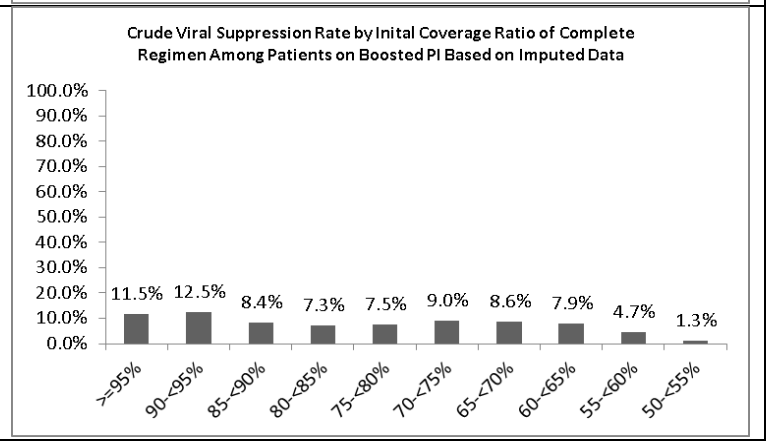
Regimen	Data Distribution (Complete Cases)	Data Distribution (One of Five Imputed Datasets)
Unboosted PI		
Boosted PI		

Figure 5.13 Distribution of Viral Suppression Rate by Change of Adherence before and after Imputation

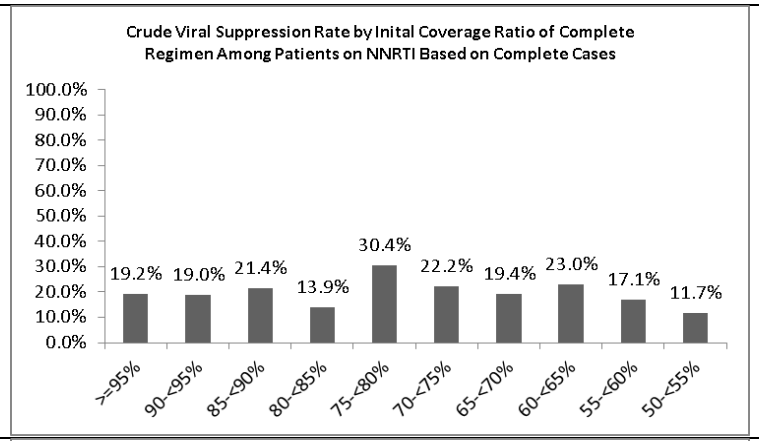
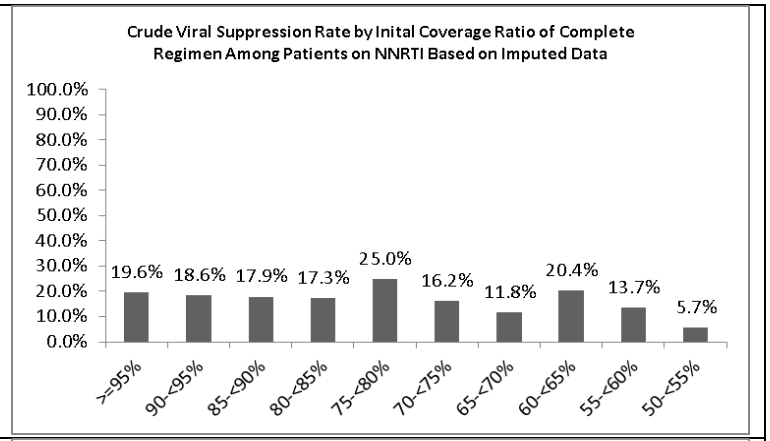
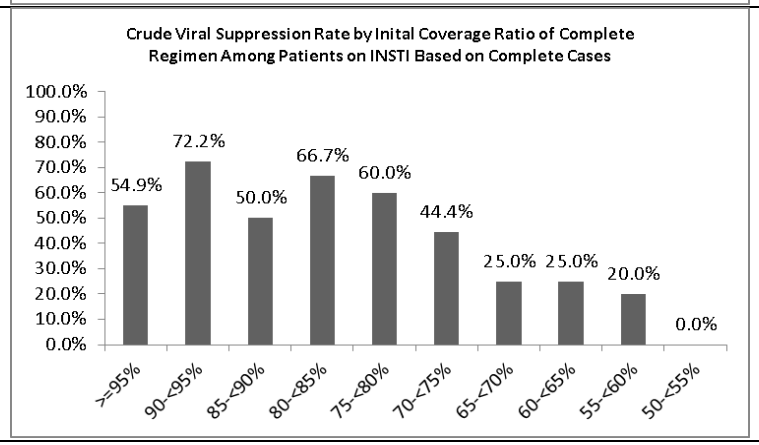
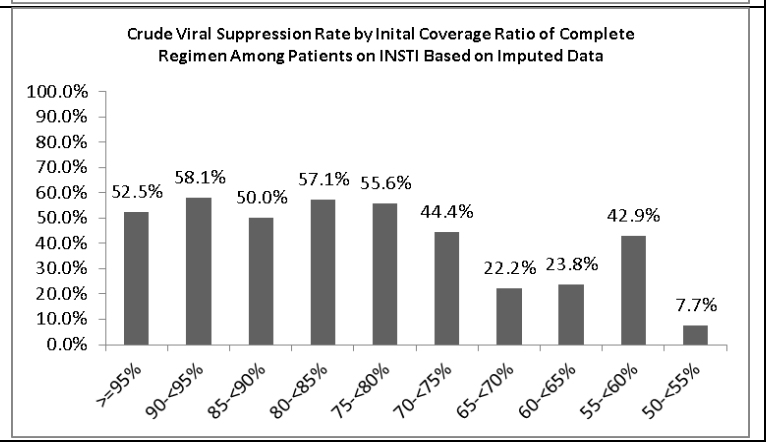
NNRTI		
INSTI		

Figure 5.13 Continued

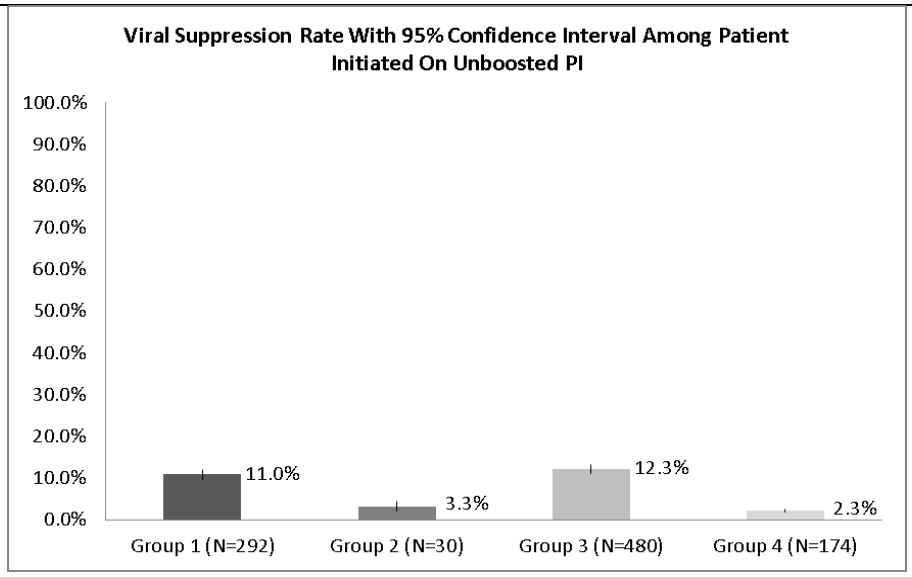
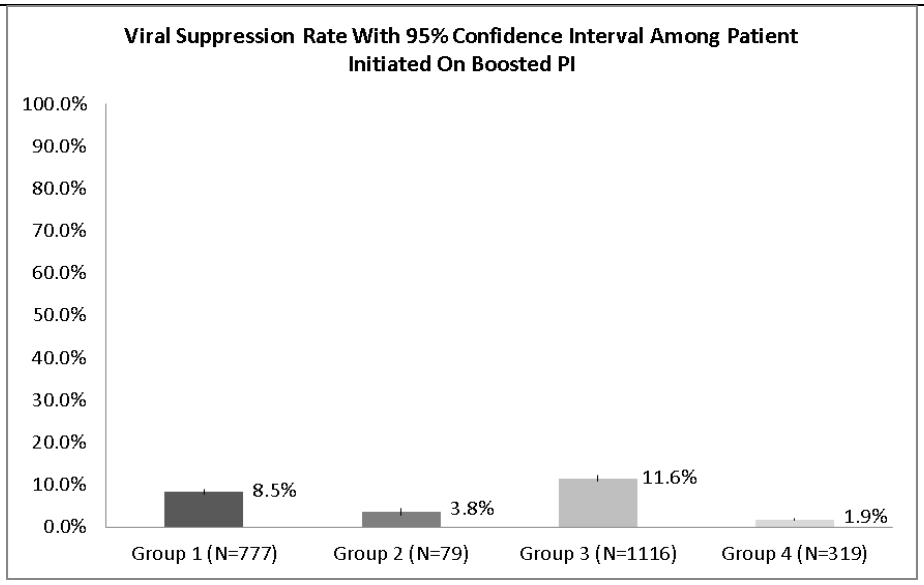
Regimen	Viral Suppression Rate With 95% Confidence Interval On One of Five Imputed Datasets
Unboosted PI	
Boosted PI	

Figure 5.14 Viral Suppression Rate with 95% Confidence Interval after Imputation

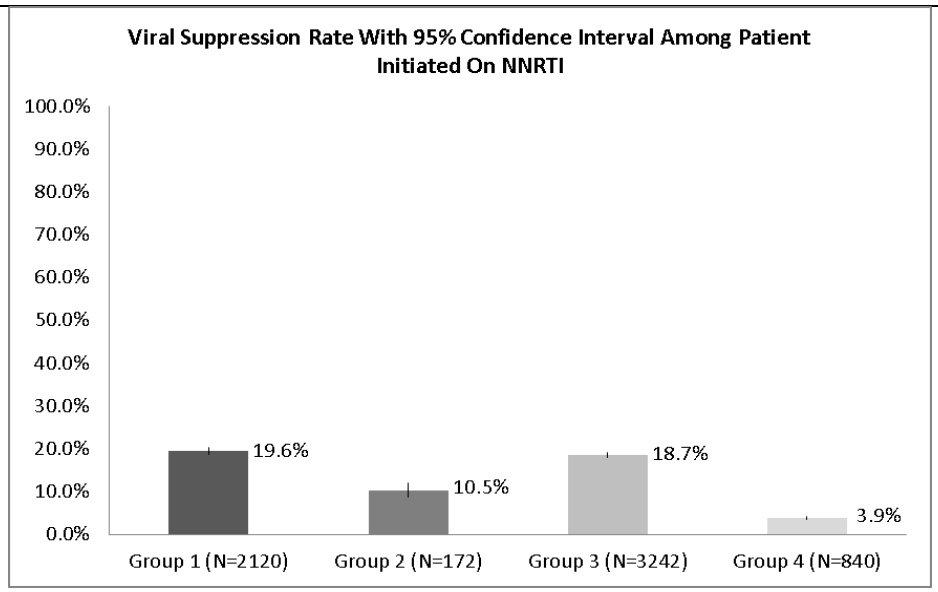
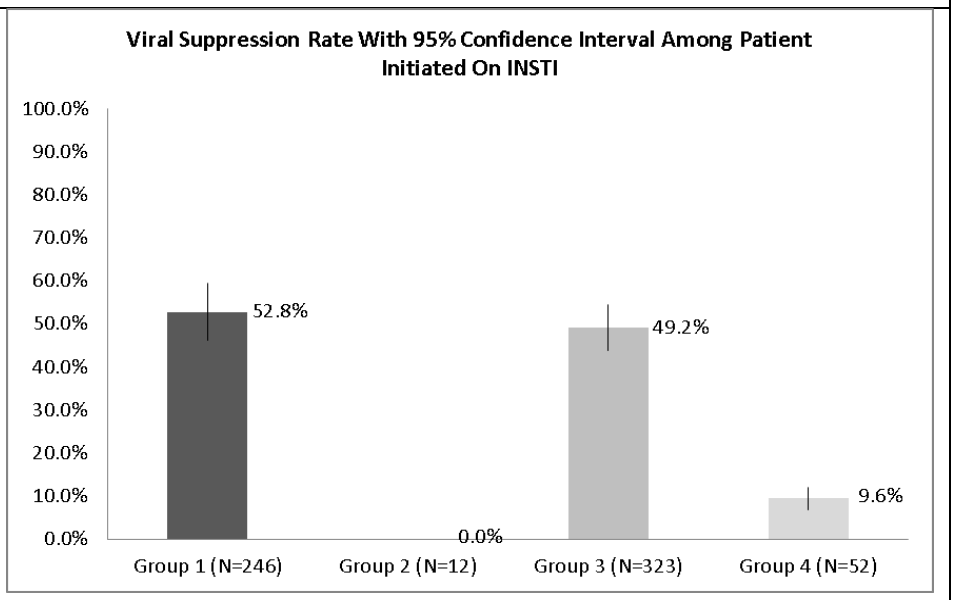
NNRTI	
INSTI	

Figure 5.14 Continued

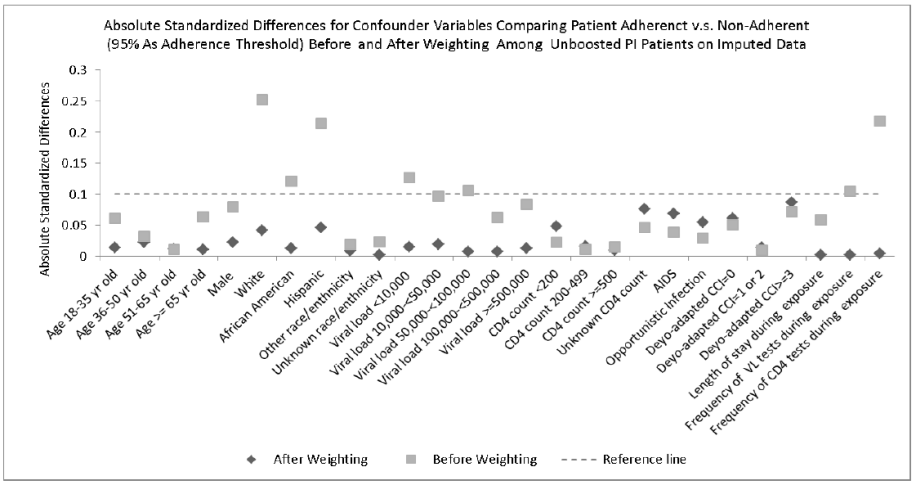
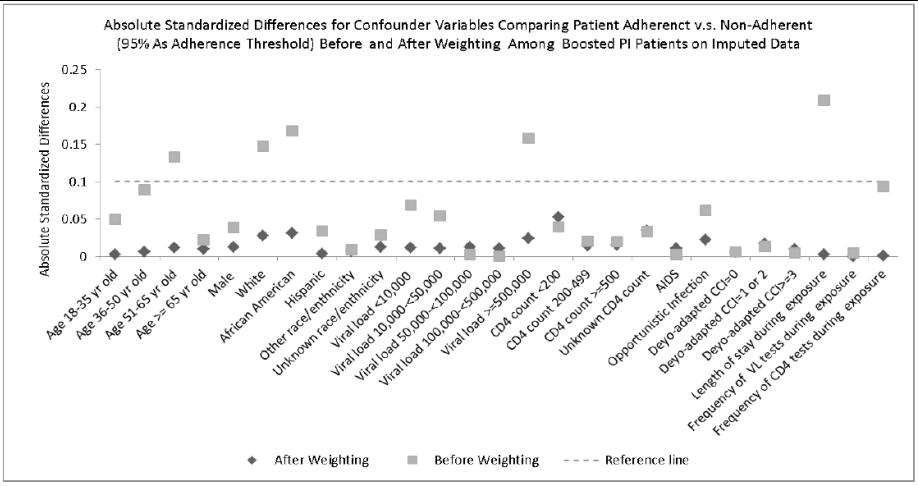
Regimen	Confounders Comparison before and after Applying IPTW
Unboosted PI	
Boosted PI	

Figure 5.15 Confounders Comparison before and after Applying IPTW Based on Imputed Data Using Adherence as Dichotomous Variable

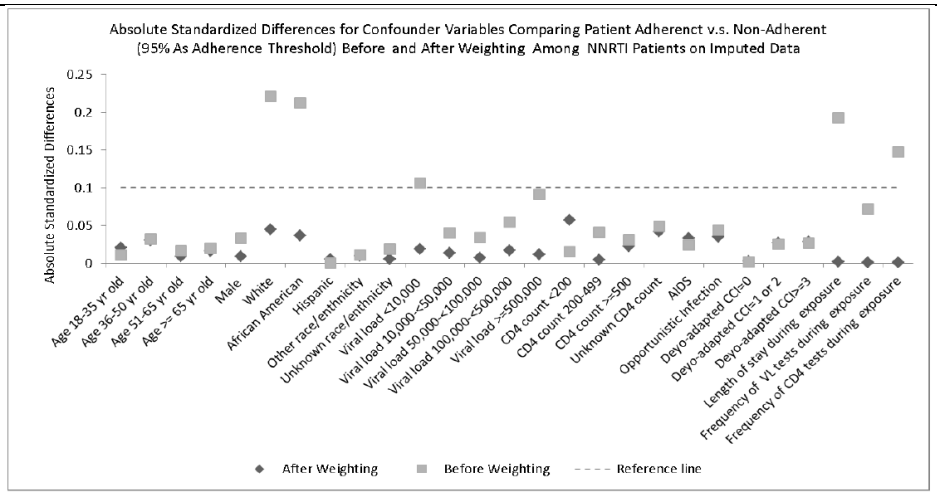
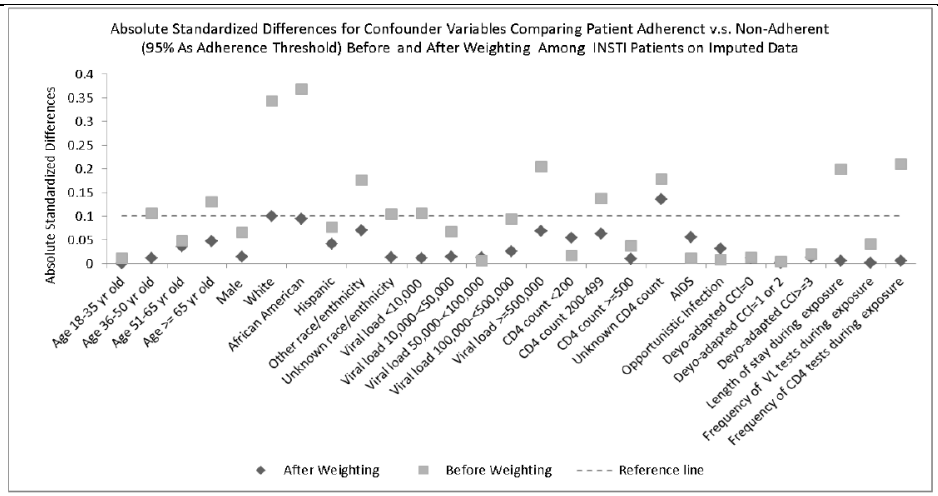
NNRTI	
INSTI	

Figure 5.15 Continued

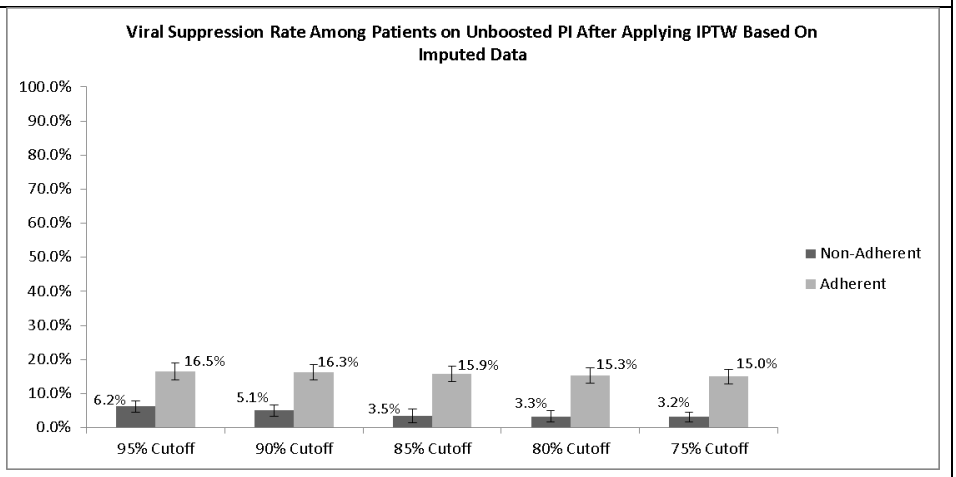
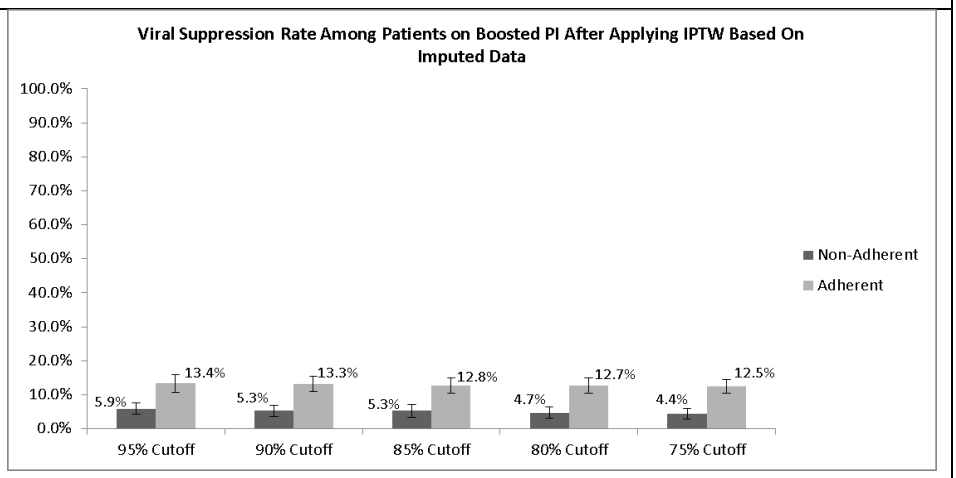
Regimen	Pooled Viral Suppression Rate after Weighting IPTW Based on Five Imputed Datasets
Unboosted PI	
Boosted PI	

Figure 5.16 Viral Suppression Rate after Weighting IPTW Based on Imputed Data

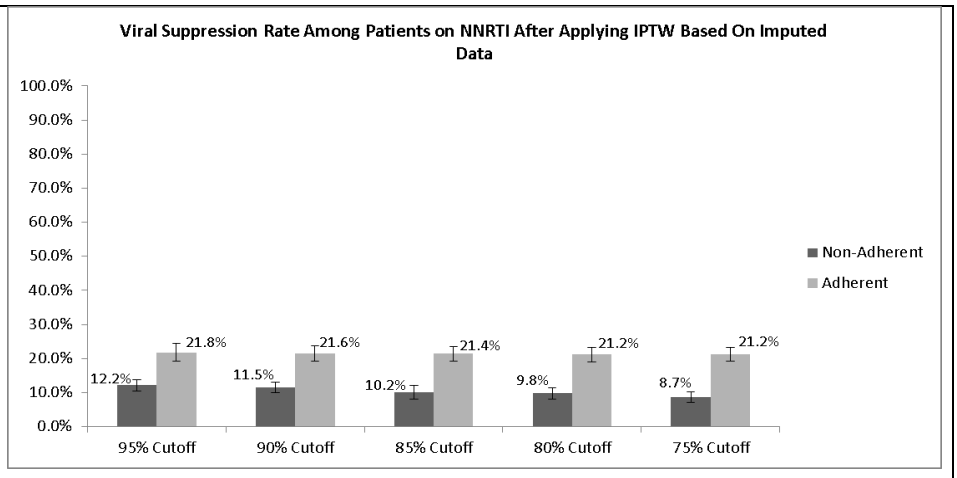
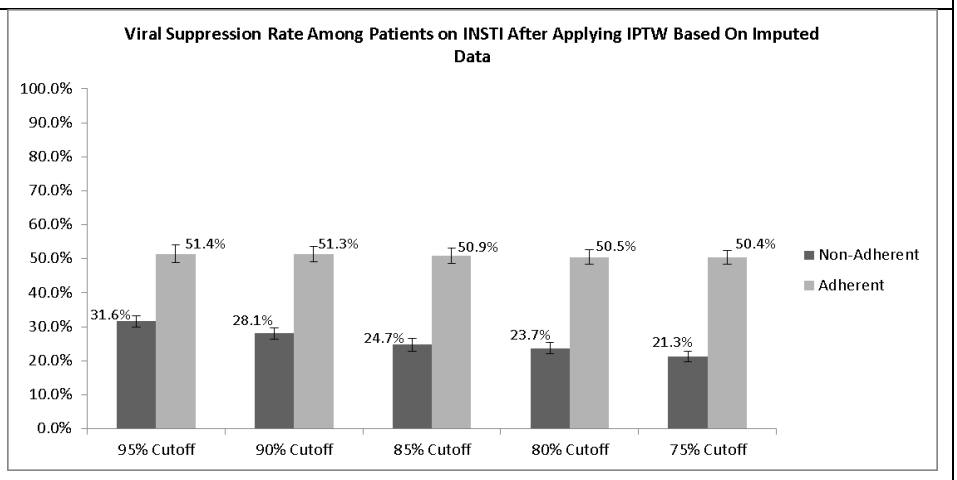
NNRTI	
INSTI	

Figure 5.16 Continued

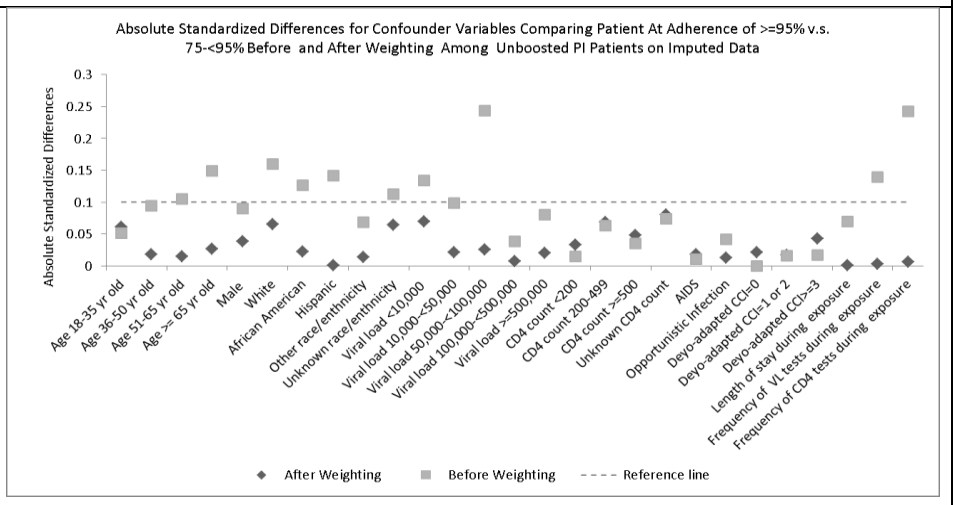
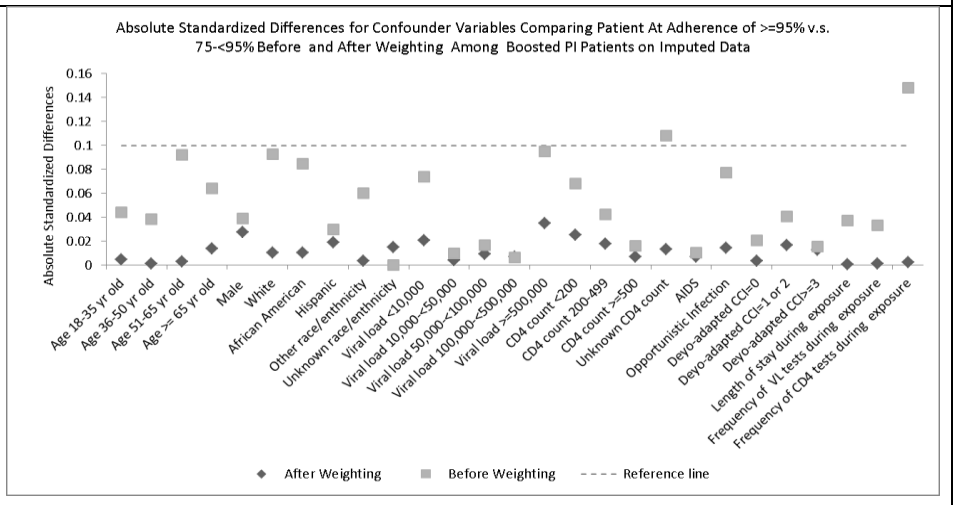
Regimen	Confounders Comparison For Adherence ≥95% vs. 75-<95%
Unboosted PI	
Boosted PI	

Figure 5.17 Confounders Comparison before and after Applying IPTW Based on Imputed Data Using Adherence as Multilevel Variable

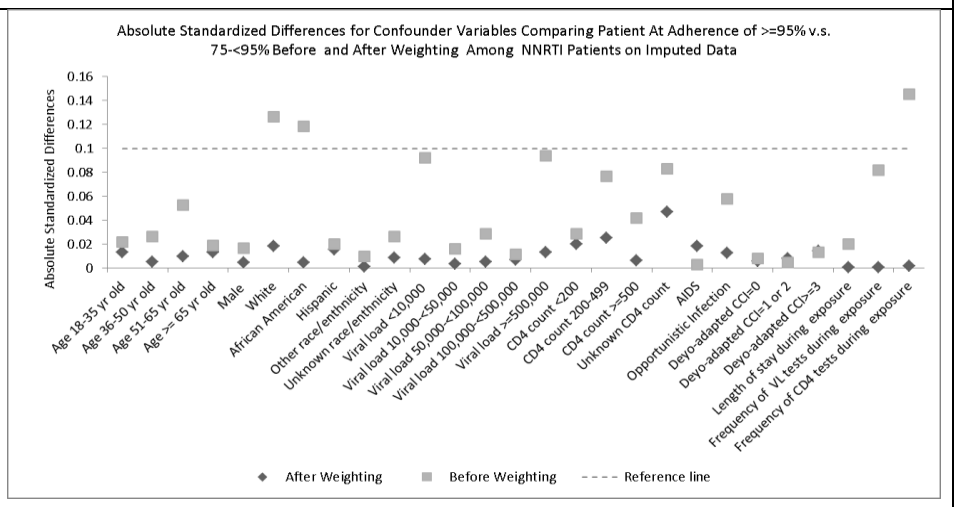
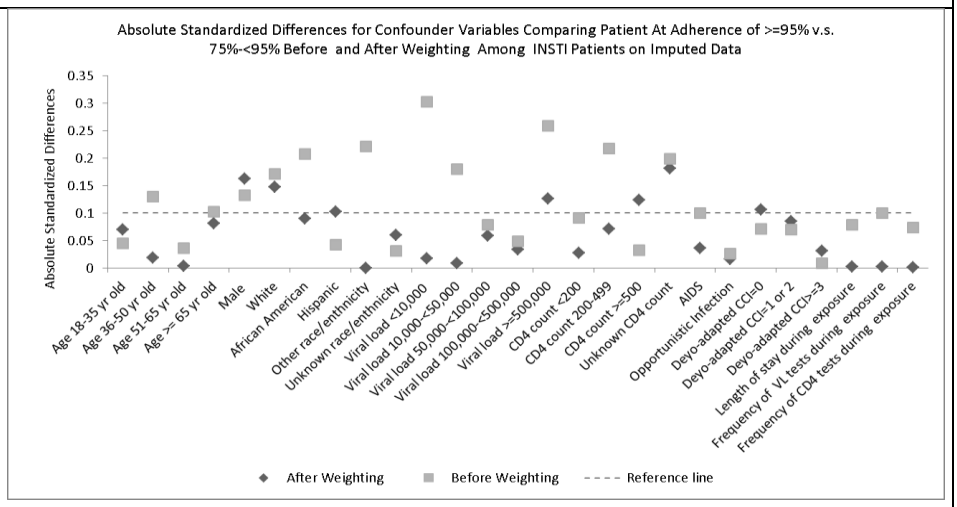
Regimen	Confounders Comparison For Adherence ≥95% vs. 75-<95%
NNRTI	
INSTI	

Figure 5.17 Continued

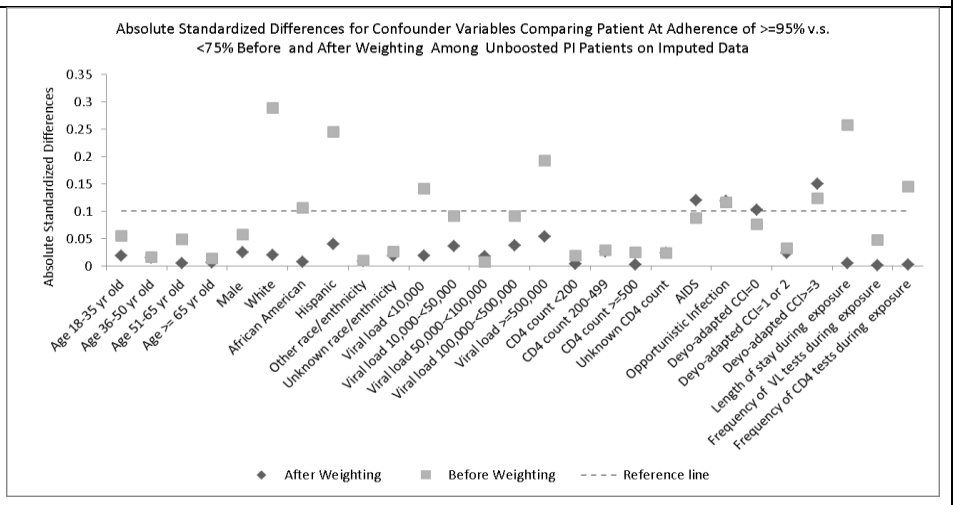
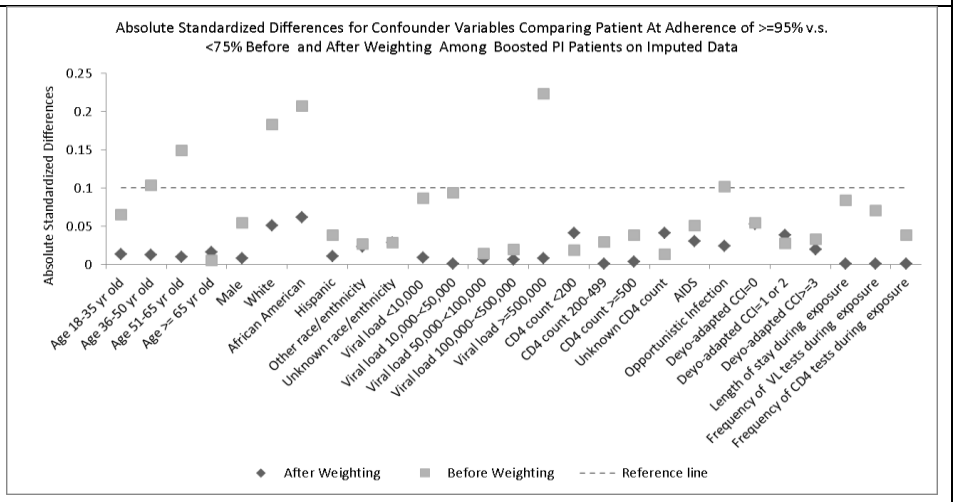
Regimen	Confounders Comparison For Adherence ≥95% vs. <75%
Unboosted PI	
Boosted PI	

Figure 5.17 Continued

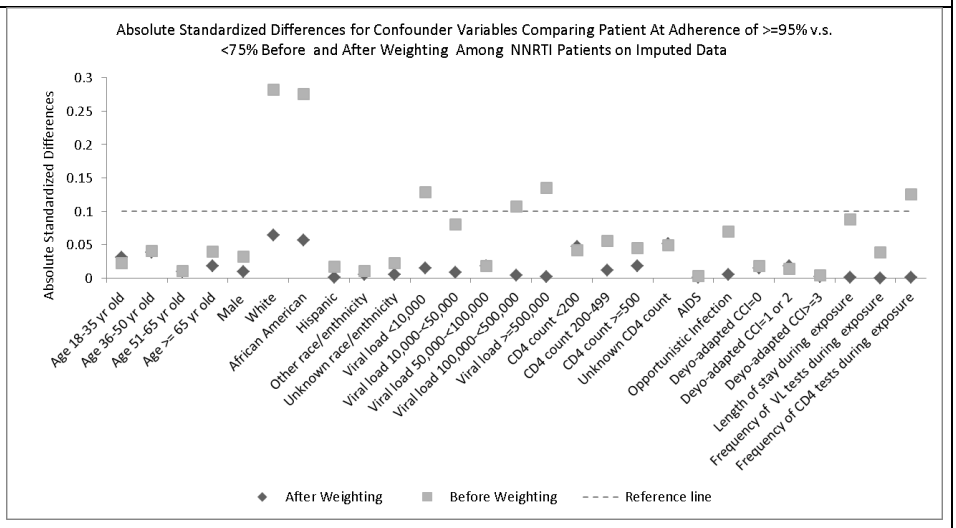
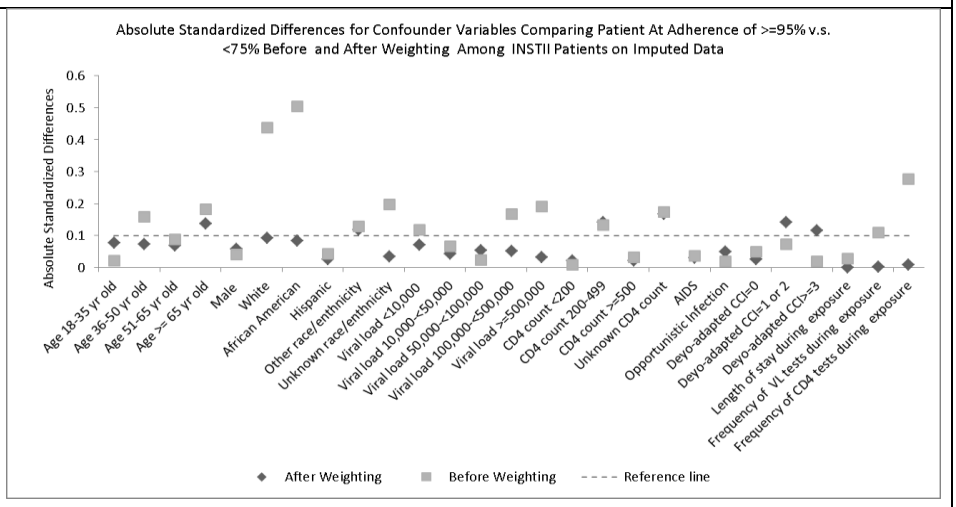
Regimen	Confounders Comparison For Adherence ≥95% vs. <75%
NNRTI	
INSTI	

Figure 5.17 Continued

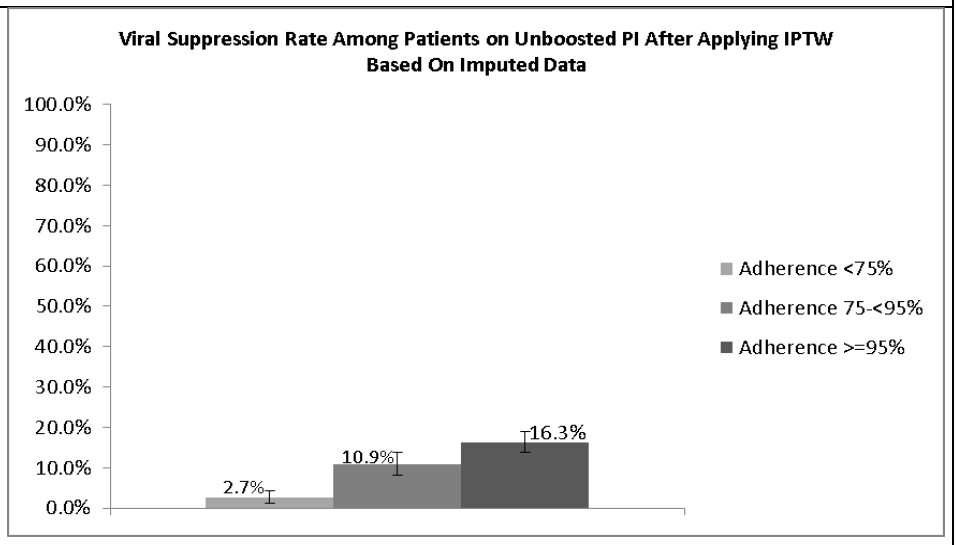
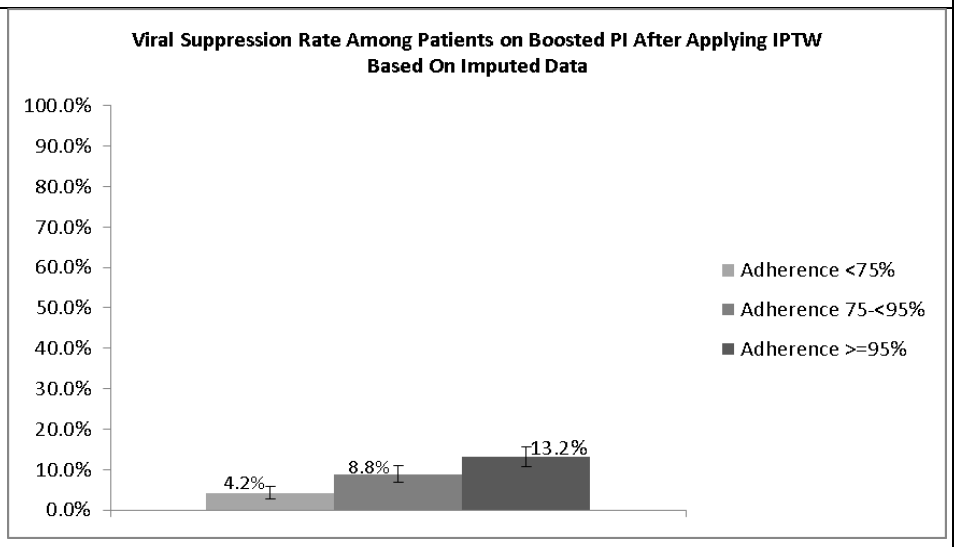
Regimen	Pooled Viral Suppression Rate after Weighting IPTW Based on Five Imputed Datasets
Unboosted PI	
Boosted PI	

Figure 5.18 Viral Suppression Rate after Applying IPTW Based on Imputed Data

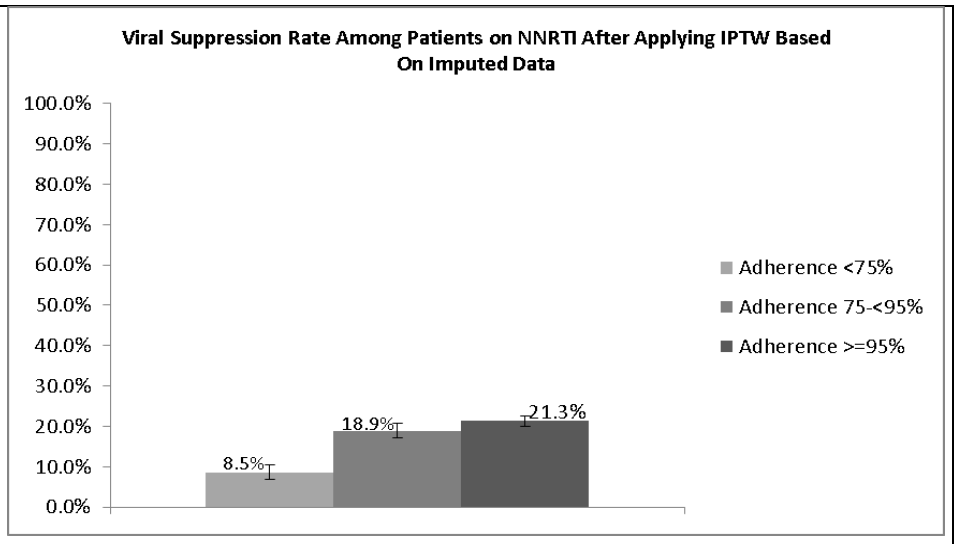
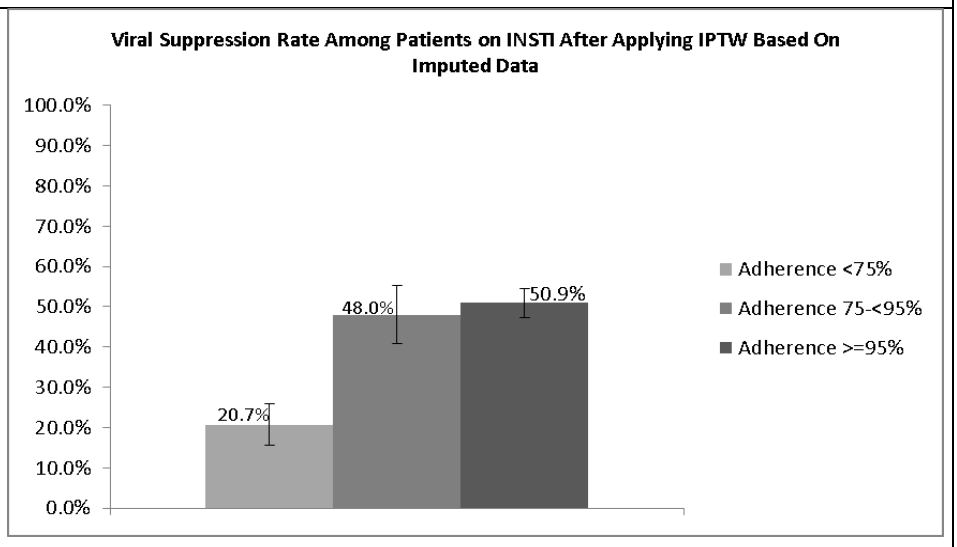
NNRTI	
INSTI	

Figure 5.18 Continued

CHAPTER 6

DISCUSSION

This study focused on exploring HIV treatment-naïve veterans' adherence and visits, and monitoring patterns and determining how patients' initial adherence (measured as initial coverage ratio) affected patients' virologic outcomes that occurred within thirty to 60 days since patients initiated ARTs.

6.1 Our Results in the Context of Previous Work

The study cohort was relatively young and healthy, and more than 50% were African-Americans. About one-third of patients had a high baseline viral load (viral load ≥ 100,000 copies/mL). One-tenth of patients initiated ARTs with a CD4 count ≥ 500 cells/mL. This reflects the US guideline's recommendations that patients should be initiated with ARTs once they are diagnosed with HIV regardless of immunosuppressive state.[5] The cohort had a very high prevalence of drug abuse (48.6%), which was very close to the prevalence rate of 50.1% reported in the HIV Cost and Services Utilization Study (HCSUS).[86] However, the cohort had a higher rate of alcohol abuse than the rate of patients who had heavy drinking that was reported in the HCSUS (29.6% vs 18.5%).[86] The cohort had a higher prevalence of mental disease than the general HIV population. The prevalence of schizophrenic disorder, depression, and psychotic disorder was 5.6%, 17.3%, and 5.4%

in our cohort compared to 3.0%, 7.5%, and 1.8%, respectively.[87] This is consistent with the finding that veterans have a higher rate of mental disease than the general population.[88] Noticeably, the cohort had a much higher rate of ischemic heart disease (IHD) than the general veterans (30.1% vs. 16.9%).[89] The literature indicates higher risk of cardiovascular events may be due to interaction between traditional risk factors and HIV infection and increased risk of thrombosis caused by endothelial dysfunctional immune activation/inflammation.[90] Another potential reason is that patients treated with ARTs have a higher risk of developing IHD.[90] The study could have mistakenly identified treatment-experienced patients as treatment-naïve patients, but strict inclusion/exclusion criterion were developed to make sure these patients were treatment-naïve.

The NNRTIs were the most commonly used regimen among the cohort, which accounted for about 62.0%, with 22.3% of patients on boosted PIs, 9.5%, of patients on unboosted PIs, and about 6.2% of patients on INSTIs. The reason that patients on INSTIs had the smallest proportion is because INSTIs were not approved on the market until 2007.[5] The study discovered that patients initiated on unboosted PIs were more likely to be male, younger, healthier, and had less severe HIV-related conditions; in comparison, patients initiated on INSTIs were more likely to be female, white, with higher baseline viral load, and with more comorbid conditions; patients initiated on boosted PIs or NNRTIs were in between. This reflects physicians' prescribing pattern and real practice in the VA setting to some degree. As the guidelines suggest, the most INSTI-based regimens are highly effective with few adverse effects and less potential for drug-drug interactions. They are recommended to most patients. [5]

The cohort had a high initial coverage ratio with the mean of 0.84–0.90 for base

agent and 0.83–0.89 for the complete regimen. Among the cohort, patients initiated on INSTIs had the highest coverage. This is because of the superiority of INSTIs in first-line HIV therapy in terms of its fewer adverse effects and better tolerance.[91] Patients initiated on PIs had the lowest coverage. This might be due to the high pill burden and treatment-associated adverse events.[5] Patients on unboosted PI have even lower adherence than those on boosted PI. The reason might be that patients on unboosted PI were younger and healthier, as patient characteristics were compared across regimens. For the thereafter one-year adherence, the same pattern was also observed. About 45.1% patient on INSTIs showed adherence levels at ≥95%; however, the proportion was only 21.2% for patients on unboosted PIs. The mean of thereafter one-year PDC of complete regimen was found to be 0.60–0.79 for various regimens. This finding is consistent with another adherence study among the US veterans treated with ARTs, which reported that the median of first year PDC to ARTs was 0.73 with the interquartile range of 0.41–0.97.[92] Due to the low genetic barrier to drug resistance and the potential for cross-resistance within the NNRTIs, patients on NNRTIs had lower thereafter one-year PDC than those on INSTIs. [5]

Regardless of initiated regimen, patients had a similar frequency of viral load and CD4 count monitoring. The mean viral load monitoring frequency in one year after the index date was 3.3 ± 1.8; however, the mean CD4 count monitoring frequency was 2.5 ± 2.0, just a little bit lower than viral load monitoring frequency. Both frequencies were lower than what the guidelines suggested. [5] The guidelines recommend to check viral load within one month after treatment initiation, every one to two months until viral load is suppressed, and then every three to four months in the first two years. They also recommend to check CD4 count within three months after treatment, then every three to six months in the first

two years. [5]

Patients' HIV office visits and length of stay for hospitalization were 7.9 times (median: 6 times) and 4.4 days (median: 0 day) on average in the first year after the index date. The distribution of both measures was similar across the regimens. Among 2,221 (21.6%) hospitalized patients, the length of stay was 20.2 days (median: 7 days) on average. Although there is no recommended HIV office visit frequency in the first year, the guidelines suggest that for frequency of viral load and CD4 count monitoring, patient visits for HIV physicians should be around six to seven times in the first year. Due to the limit of data that could be obtained, nothing is known about the missed office visits for these patients. One study has evidenced that missed office visits would significantly increase mortality risk among US population with HIV.[93] The hospitalization rate of the present cohort is similar to the study of the HIV Research Network (HIVRN) cohort composed of adult patients with HIV in the US, which reported a hospitalization rate of 22.2%.[94] However, the mean of total length of stay in one year for the HIVRN cohort who were hospitalized was about 12.9–13.9 days during 2000 to 2002, which was shorter than this study's cohort. [94] This might be caused by a proportion of veterans who had extremely long length of hospitalization more than 300 days, since the median length of stay for the study cohort was only about 7 days.

The initial coverage ratio of base agent and complete regimen were highly correlated. However, the correlations between initial coverage ratio and thereafter one-year PDC were low. One previous study has shown that it is hard to distinguish patients who would be not adherent to ARTs based on patients' baseline characteristics.[78] This finding further confirms that short-term adherence does not well predict long-term adherence either.

The present findings also show interaction between adherence and type of regimens, which means ARTs have an influence on long-term adherence. For example, if patients' initial adherence was low and they were also initiated on a PI-based regimen, then patients were more likely to be at low adherence; in comparison, if patients' initial adherence was high and they were initiated on NNRTI-based regimen, then patients were more likely to be at high adherence. These suggested that regimens' side effects and barriers to drug resistance may influence long-term adherence.

Patients who were African-Americans and had a low social economic status, low baseline viral load, and high baseline CD4 counts consistently had lower adherence than other patients across all regimens. These findings were consistent with the results of other published studies. Evidence showed that racial disparities exist in HIV treatment adherence, and African-Americans had the lowest adherence of all races, including whites and Latinos.[95] A meta-analysis study reported that patients who did not perceive their disease as severe or as a threat were >1.5 times more likely to be nonadherent.[96] The present study found that patients who had missing outcomes shared the similar characteristics with patients at low adherence levels.

In the pseudo-population, regardless of the threshold to define adherent, adherent patients had similar viral suppression rates for each regimen category: 15.0–16.5% for unboosted PIs, 12.5–13.4% for boosted PIs, 21.2–21.8% for NNRTIs, and 50.4–51.4% for INSTIs. However, when the viral suppression rate differences between adherent and nonadherent patients using various thresholds were compared, findings were different. It seems that the 85% threshold matters for unboosted PIs, since after that, lower adherence does not affect the viral suppression rate; but for the other regimens, the relationship

between adherence and viral suppression rate of nonadherence has a linear trend. When adherence was measured as a categorical variable, medium adherence was found to have the biggest effect on viral suppression rates among patients on unboosted PIs, followed next by boosted PIs. However, for patients on NNRTIs and INSTIs, there was an almost obvious difference in viral suppression rates between patients at medium adherence and at high adherence. These findings suggest adherence affected viral suppression rate variously by regimen class. For PI-based regimens, medium level adherence would have significant effects on viral suppression; but for NNRTI- or INSTI-based regimens, adherence might not significantly influence adherence, until adherence is reduced to the lowest level. These findings are similar to what was reported in the literature that the 95% threshold might not be necessary and adherence works differently on viral suppression rate for various regimens.[27,29,30,37,73,74,97] However, all of the current findings suggest a 95% threshold for adherence is not necessary. Due to the limited sample size, dividing adherence into more than 3 levels could cause positivity issue (not enough sample size) to estimate adherence effect; therefore, an adherence effect could not be estimated when adherence was evenly divided into narrower adherence categories.

In the MSM models, regardless of threshold to define adherence, adherent patients had significantly higher viral suppression rate than nonadherent patients. Patients at medium adherence had a significantly reduced rate of viral suppression for PI-based regimens, but not for NNRTI- or INSTI-based regimens. Across all regimens, low adherence was more consistently associated with a reduced viral suppression rate than high adherence.

Interestingly, patients on INSTIs consistently had the highest viral suppression rate

no matter what adherence level patients were at, followed by the patients on NNRTIs, and then those on PIs. For example, patients on INSTIs with adherence <75% still had a viral suppression rate of 20.7%, which was the same as the rate for patients on NNRTIs with adherence ≥95% and higher than the rate for the patients on PIs with adherence ≥95%. However, this may not indicate that INSTIs would be more potent than PIs and NNRTIs. It is because the patients initiated with different regimens had different characteristics, which made the adherence effects not comparable across the regimen categories.

6.2 Strengths

This study helped to understand how the HIV treatment-initiated veterans were treated and monitored, as well as how they used the health care through the VHA system within one year after treatment initiation.

Multiple methods to measure patient adherence were applied, including coverage ratio and PDC for both a base agent and a complete regimen.

The study also added the evidence that it would be hard to predict patients who would potentially have poor adherence in the future just according to the patients' initial adherence, since the correlation between these two measures is so weak.

Moreover, our study applied an IPTW approach, a causal inference method to address confounding bias and to identify the causal effects of initial adherence to different HIV regimens on virologic outcomes among veterans with HIV-1. The present was a comprehensive study that investigated the various first-line regimens, including unboosted/boosted PI-, NNRTI-, and INSTI-based regimens.

Different from previous studies, adherence effects were estimated via traditional

relative risk estimate (i.e., odds ratio); figures were also created to display viral suppression rates based on a pseudo-population after balancing confounders between comparison groups.

Sensitivity analyses were also conducted to assess the robustness of study results. For example, multiple methods were used to define viral suppression, including definition by the guidelines or viral load <50 copies/mL, and also some other thresholds to define a good virologic outcome, i.e., viral load <200 copies/mL or viral load <400 copies/mL. As for the initial adherence, different methods were also used to measure it, including calculating it as a continuous variable, dichotomizing it into a binary variable via selecting different thresholds, and categorizing it into a categorical variable with three levels.

Finally, this study did not simply exclude patients who had missing outcomes similar to what previous studies have done, but applied imputation techniques to impute the outcome. The purpose of doing this was to avoid selection bias, which was especially true if patients who had missing outcomes were more likely to be those who had poor adherence. This has been confirmed when patient characteristics were compared between patients with or without missing outcomes.

6.3 Limitations

Since this is a retrospective study based on an existing database, some limitations are unavoidable. The first limitation is related to the inclusion/exclusion criteria. Although rules were made to maximally exclude patients that would be treatment-experienced, it is still possible to misclassify patients.

Second, adherence was calculated according to refill records, which might not

really reflect patient adherence behavior. And although unlikely, there is a possibility that patients obtained medications outside the VHA system.

Third, an assumption was made to calculate initial adherence. If there was no second fill of base agent within 60 days, patients were assumed to have discontinued the regimen, resulting in a calculation of patients' initial coverage ratio of base agent as 0.5. This is the conservative way to calculate adherence, since these patients are highly likely to have even lower adherence or do not take ARTs at all.

Forth, this study is a short-term study focused on exploring the causal effects of initial adherence on virologic outcomes that occurred during thirty to 60 days after treatment initiation. So, findings might not be generalizable to the long-term effect of adherence, or to treatment-experienced patients. Additionally, the study results might not be generalizable to a more general population outside the VHA system.

Fifth, an IPTW approach was applied to address confounding bias. This technique requires three assumptions: consistency (an individual potential outcome under the observed exposure history is precisely the observed outcome), positivity (nonzero probability of receiving every level of exposure for every combination of values of exposure and covariates), and exchangeability (no unmeasured confounders).[98] However, some assumptions are untestable. For example, if there are potentially unknown confounders, then IPTW could not remove confounding bias, even if the all observed confounders become balanced between comparison groups after weighting. Actually, even though IPTW weighting was conducted, balance could not be achieved for some specific regimens (i.e., INSTI-based regimen) due to limited sample size. This should be kept in mind when making decision based on the study results.

Sixth, outcomes were imputed for patients who had missing values. The imputed value might not be the same as true observations if virologic outcomes were captured during that specific time period. However, more than one method to impute data was tried, in addition to comparing data before and after imputation to make sure the imputed outcomes were as close to the truth as possible.

Seventh, due to a limited data source, variables could not be captured that were related to the present study, such as patients' medical literacy, missing of scheduled HIV office visits, HIV/AIDS-caused hospitalizations, and bio-markers of HIV, or HIV severity index. Besides, this study only evaluated the adherence effects on virologic outcome without considering time to event. That is because, in this study, time to event depended on when the viral loads were measured, which would not reflect the exact time when patients achieved viral suppression.

Eighth, lab data from the VHA contained hundreds and even thousands of different lab names for viral load and CD4 count tests. The test values were also not well structured, including both text and numeric values. The algorithm that we used might have potentially missed some tests or lab values that should have been included.

Last but not least, we built models for each regimen category, respectively. Patients initiated with different regimens might have different characteristics. So the adherence effects on viral suppression might not be comparable across regimens.

6.4 Conclusions, Implications, and Future Research

In general, the HIV treatment of newly-initiated patients initiating ART were well monitored in the first year in terms of viral load and CD4 count test frequency, as well as

office visits. The hospitalization rate of the cohort was similar to the estimate of the HIVRN cohort composed of adults with HIV in the US, but with longer stays among the hospitalized patients in the average, due to a proportion of veterans who had extremely long stays. Although the initial coverage ratio of base agent and complete regimen were highly correlated, the correlations between initial coverage ratio and thereafter one-year PDC were low, which indicated that patients' long-term adherence could not be predicted by their short-term adherence alone. Compared to NNRTI- and PI-based regimens, INSTI-based regimens were most potent, achieving the highest viral suppression rate, even among the patients who had poor adherence. Lower adherence caused lower viral suppression rates, with the association differentiated by the regimen. Due to limited sample size in each regimen category, classifying adherence level into more than three levels would cause few observations in some levels. Although it was still hard to clearly understand if the association between adherence and viral suppression was linear, had a threshold somewhere, or a combination of both, the present study found that patients on PI-based regimens were more likely to fail to achieve viral suppression at a higher adherence threshold than other regimens.

The study could have many implications. First, although the initial coverage ratio could not perfectly predict patients' long-term adherence, the correlation between them was in the range of 0.54–0.63, indicating medium strength. Correlations between the initial adherence and thereafter adherence were found to be different depending on which regimens that patients were on. All these suggest that it is valuable to include baseline adherence and the nature of regimen (i.e., treatment effectiveness, side effects, barrier to drug resistance) as the important predictors to predict patients' long-term adherence.

Second, in comparison, patients on PIs are more likely to move to a lower adherence category, which suggests more attention should be paid to patients who were treated on PIs. Some interventions should be initiated to improve adherence of this group specifically.

Third, the present study does not support the 95% threshold to be as important as suggested in the guidelines, since viral suppression rate among patients with adherence level of ≥75% was very similar to the rate among those with adherence level of ≥95%. Besides, although patients with medium adherence (75-<95%) did not have a significantly reduced rate compared to patients with high adherence (≥95%), the differences between them were still clinically significant. Therefore, keeping patients' adherence level as high as possible is important to maximize the possibility of achieving viral suppression.

There are still many questions that need to be answered in future studies. It remains unknown if missing scheduled HIV office visits potentially influences patient virologic outcomes. HIV veterans had a longer length of stay, even though the hospitalization rates were similar between them and the US general population. That difference should also be explored. Further studies should investigate why patients on each specific regimen category had a lower adherence, including the reason that patients had a low adherence at baseline, and why so many patients who had a high initial adherence eventually moved to lower-adherence category. Finding-based interventions should be initiated among these patients. Future studies should apply more advanced technology, such as natural language process (NLP), to identify HIV labs and their values in medical notes to add more data and improve the data accuracy in our study. The present study only explored the effect of initial adherence on viral suppression, with the consideration of avoiding time-dependent

confounding bias. Futures studies should explore the long-term effect with addressing time-dependent confounding bias, or the adherence effect on the time to event, or some other outcomes of interest such as immunologic outcomes, viral rebound, hospitalization caused by HIV/AIDS, death, drug resistance, or quality of life. More advanced methods should be applied to identify the causal effect of continuous adherence or delayed filling days on either categorical or continuous outcomes (i.e., viral load or CD4 counts). The study censored patients when they switched the initiated regimen. Future studies could apply a dynamic treatment regimes approach to understand how the different treatment strategy combined with different starting adherence level would influence outcomes. Future studies also need to explore the adherence effects among treatment-experienced patients.

In summary, this study showed how initial adherence differently influenced the viral suppression rate across different regimens. No evidence shows 95% adherence threshold is necessary. Patients with medium adherence (75-<95%) can achieve viral suppression with the rate not statistically significantly different from patients with high adherence.

APPENDIX

SENSITIVITY ANALYSES

A.1 Analyses Based on Patients Who Did Not Have Missing Outcomes

We only do analysis for dichotomized adherence. The reason that we do not do analysis for adherence at three levels is because of positivity issues, since there is a lack of observations for some cells.

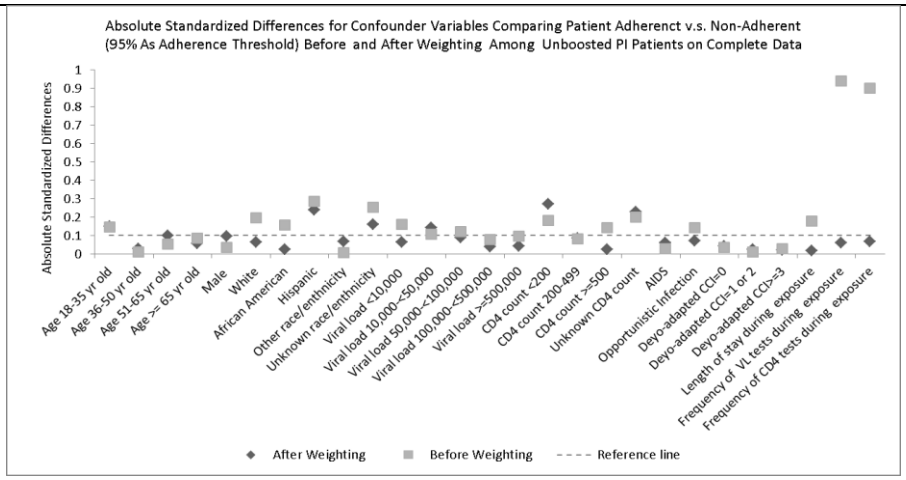
Regimen	Confounders Comparison before and after Applying IPTW
Unboosted PI	

Figure A.1 Confounders Comparison before and after Applying IPTW Based on Complete Cases with Using Adherence as Dichotomous Variable

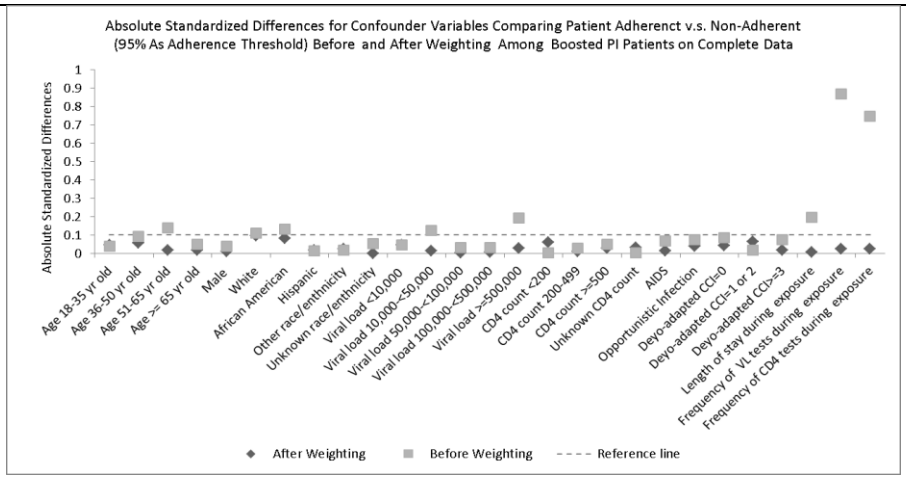
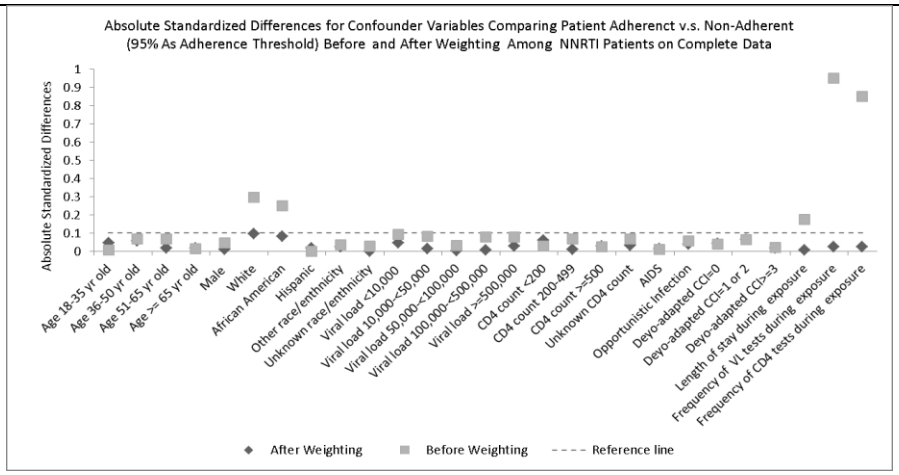
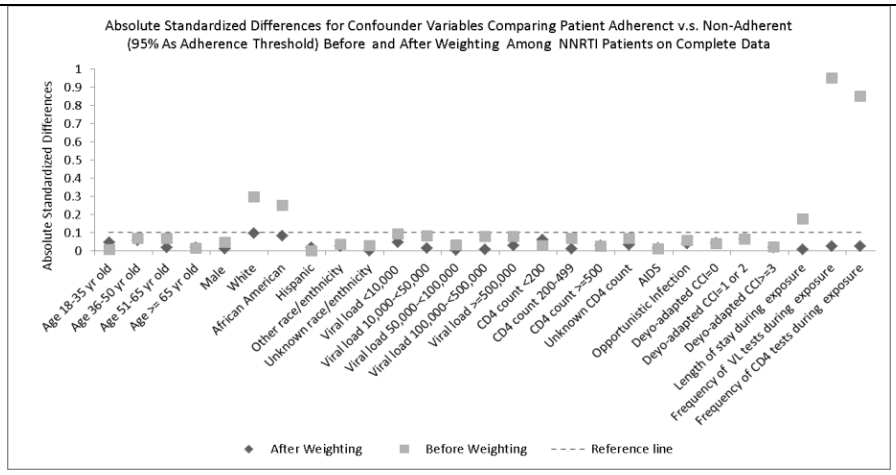
Regimen	Confounders Comparison before and after Applying IPTW
Boosted PI	
NNRTI	
INSTI	

Figure A.1 Continued

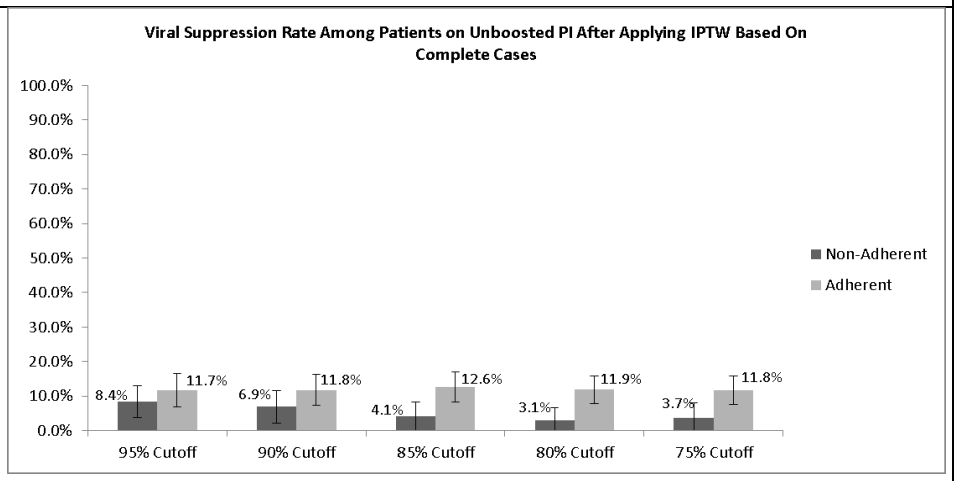
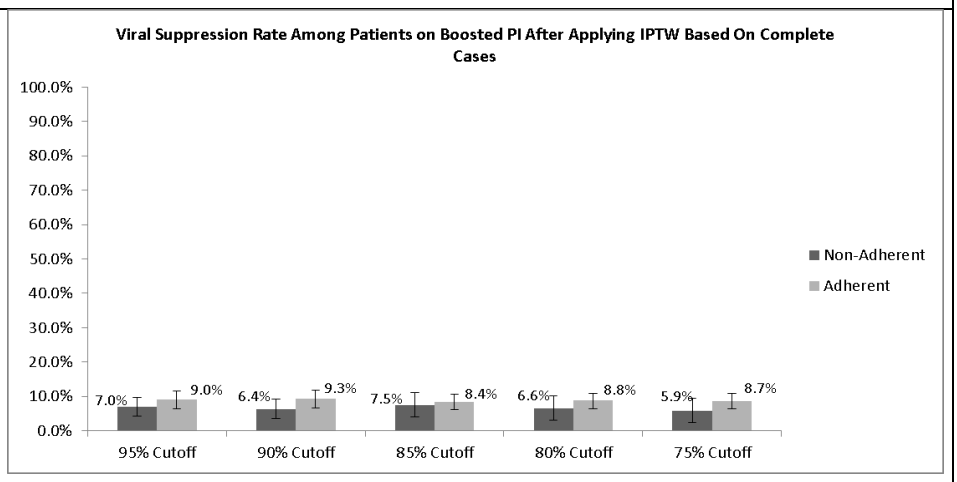
Regimen	Viral Suppression Rate after Weighting IPTW Based on Completed Cases
Unboosted PI	
Boosted PI	

Figure A.2 Viral Suppression Rate after Weighting IPTW Based on Completed Case

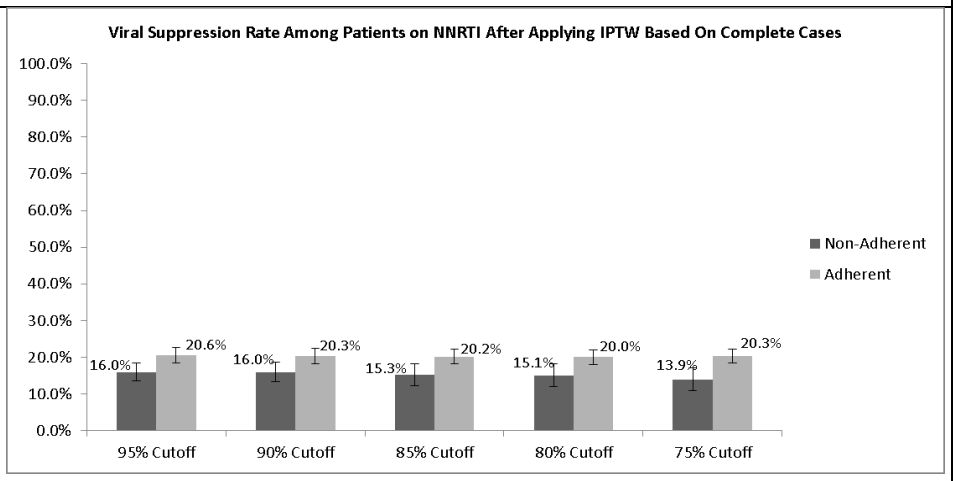
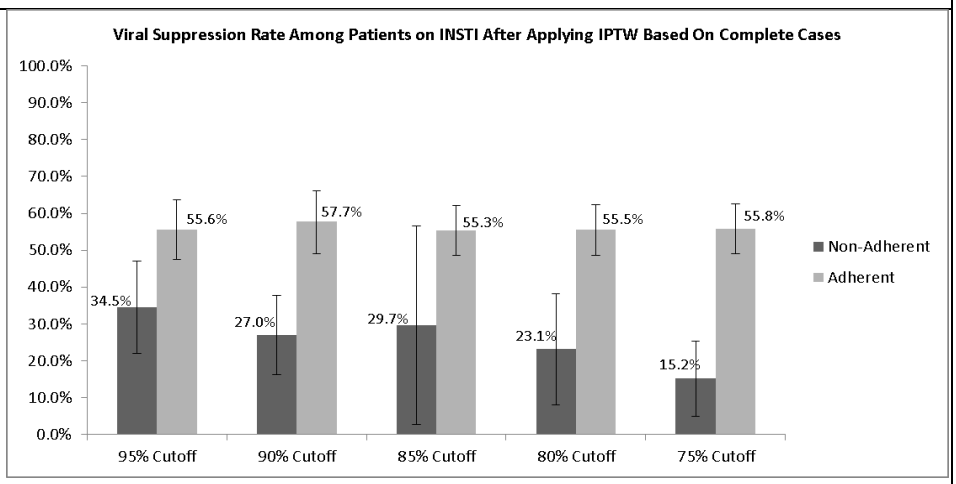
Regimen	Viral Suppression Rate after Weighting IPTW Based on Completed Cases
NNRTI	
INSTI	

Figure A.2 Continued

A.2 Analyses for Virologic Outcome Defined as Viral Load < 50 Copies/mL, < 200 Copies/mL, < 400 Copies/mL Based on Imputed Data

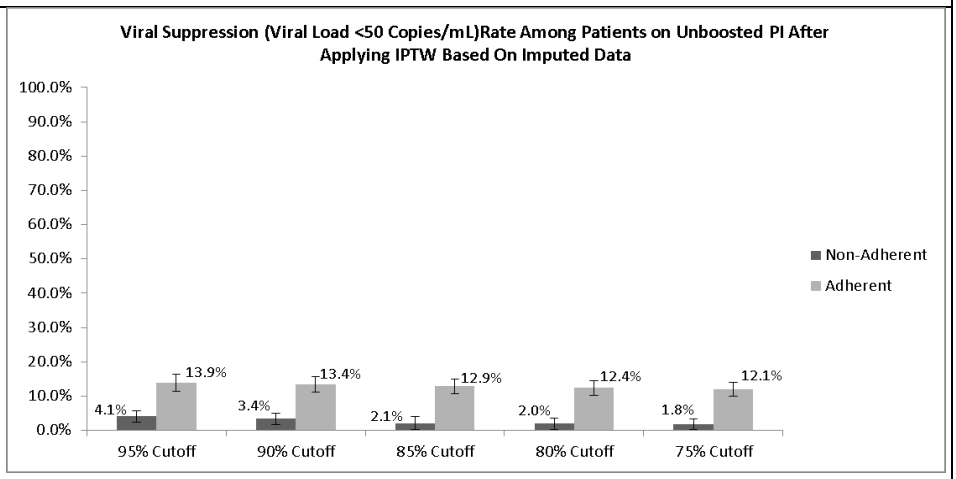
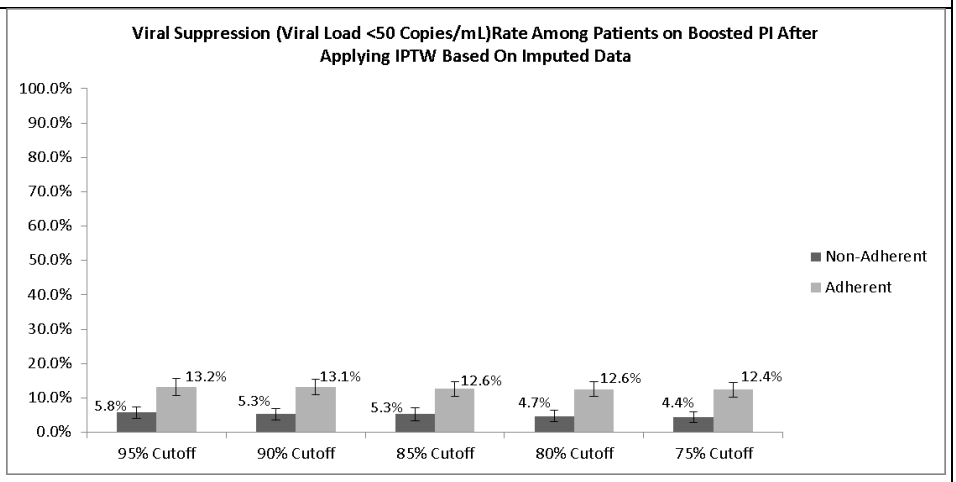
Regimen	Pooled Rate of Viral Load < 50 Copies/mL after Weighting IPTW Based on Five Imputed Datasets
Unboosted PI	
Boosted PI	

Figure A.3 Rate of Viral Load < 50 Copies/mL by Dichotomized Adherence after Weighting IPTW Based on Imputed Data

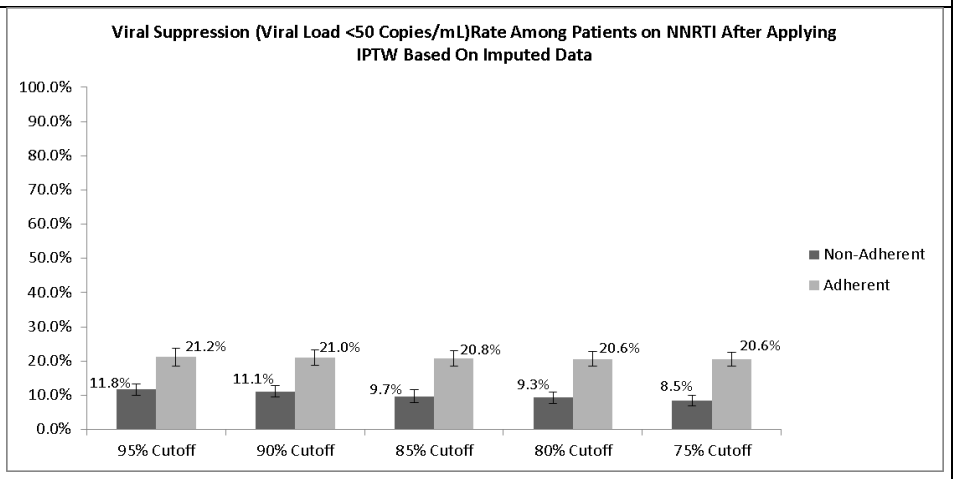
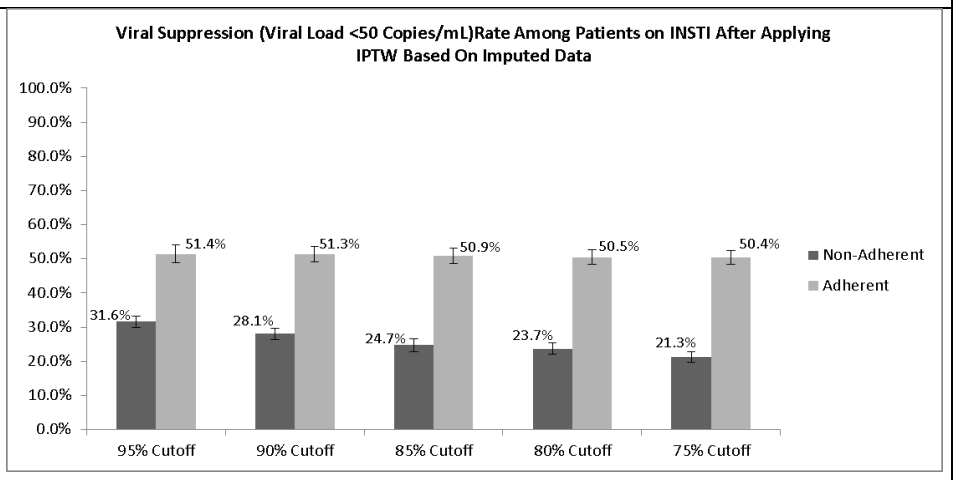
Regimen	Pooled Rate of Viral Load < 50 Copies/mL after Weighting IPTW Based on Five Imputed Datasets
NNRTI	
INSTI	

Figure A.3 Continued

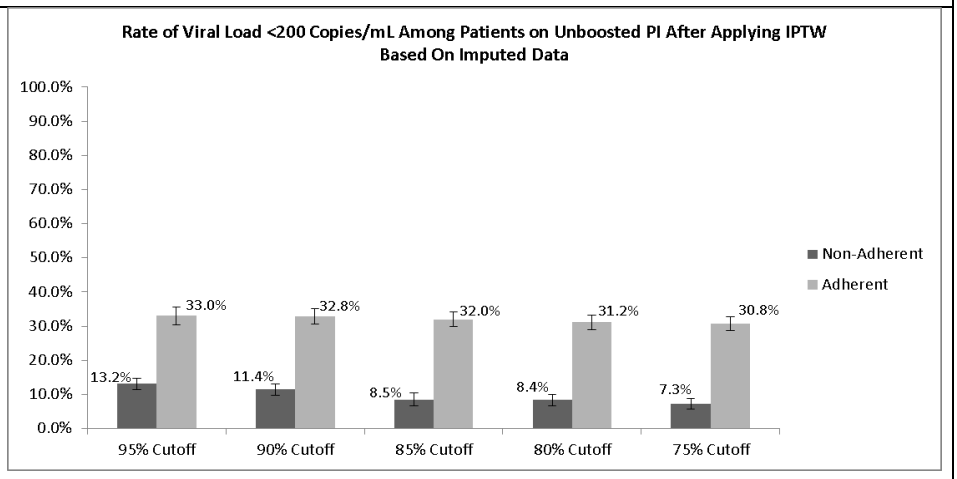
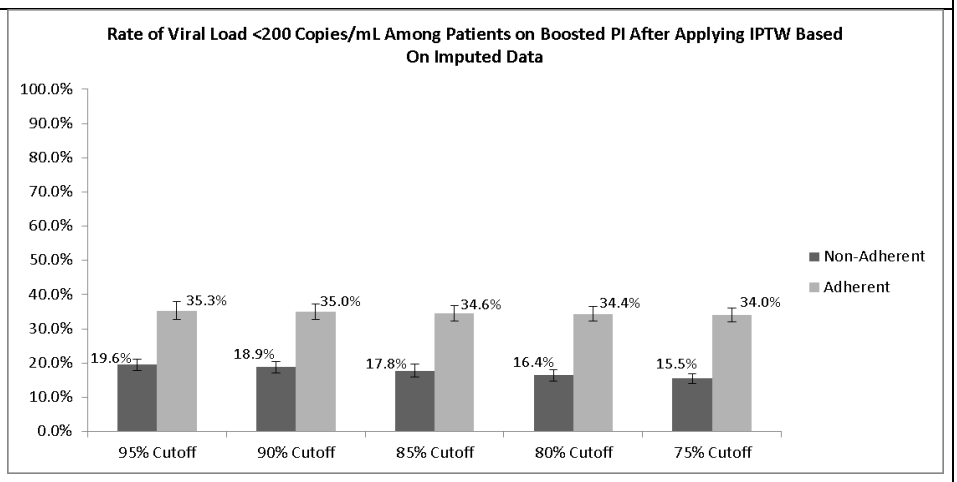
Regimen	Pooled Rate of Viral Load < 200 Copies/mL after Weighting IPTW Based on Five Imputed Datasets
Unboosted PI	
Boosted PI	

Figure A.4 Rate of Viral Load < 200 Copies/mL by Dichotomized Adherence after Weighting IPTW Based on Imputed Data

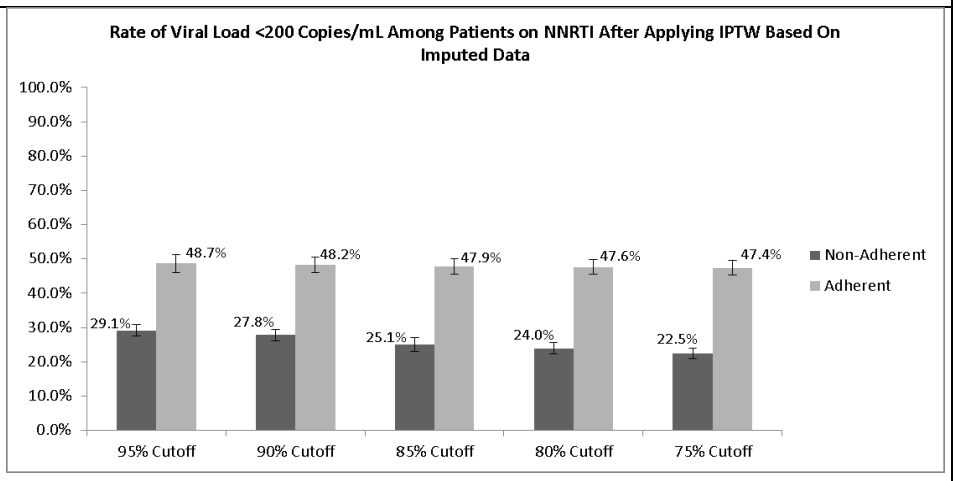
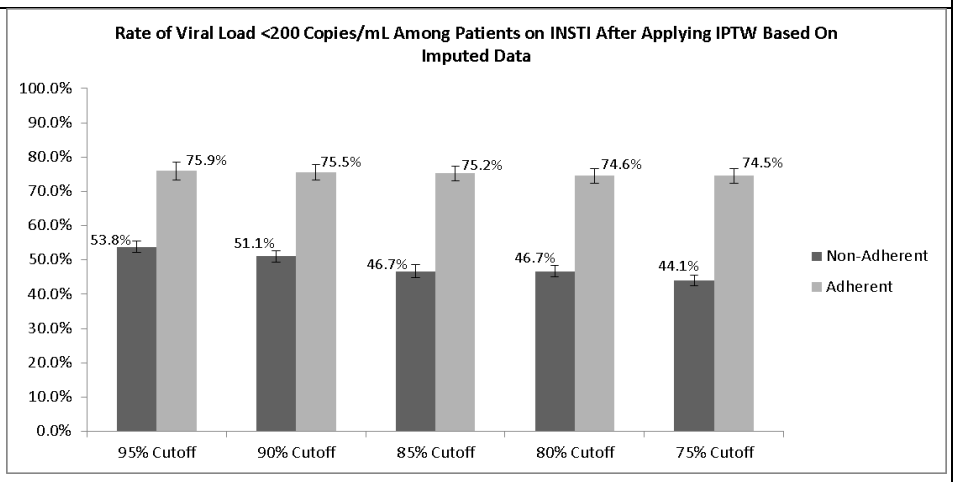
Regimen	Pooled Rate of Viral Load < 200 Copies/mL after Weighting IPTW Based on Five Imputed Datasets
NNRTI	
INSTI	

Figure A.4 Continued

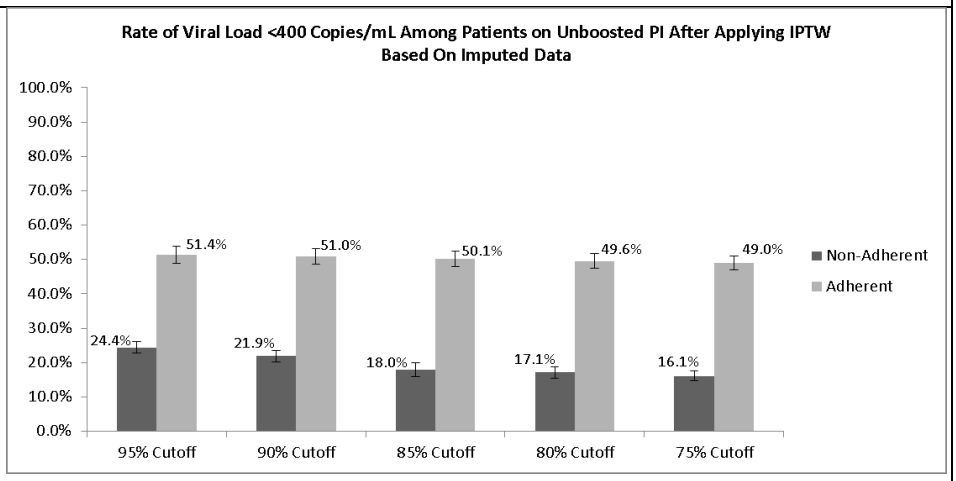
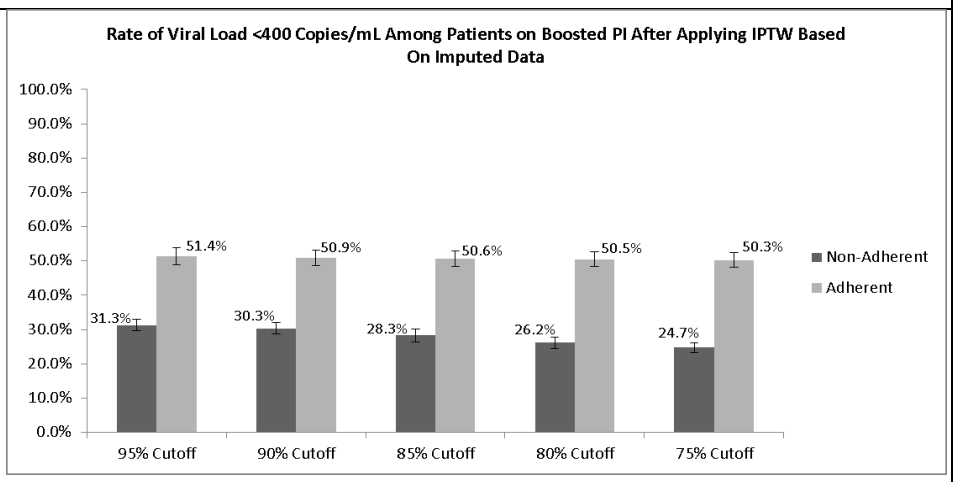
Regimen	Pooled Rate of Viral Load < 400 Copies/mL after Weighting IPTW Based on Five Imputed Datasets
Unboosted PI	
Boosted PI	

Figure A.5 Rate of Viral Load < 400 Copies/mL by Dichotomized Adherence after Weighting IPTW Based on Imputed Data

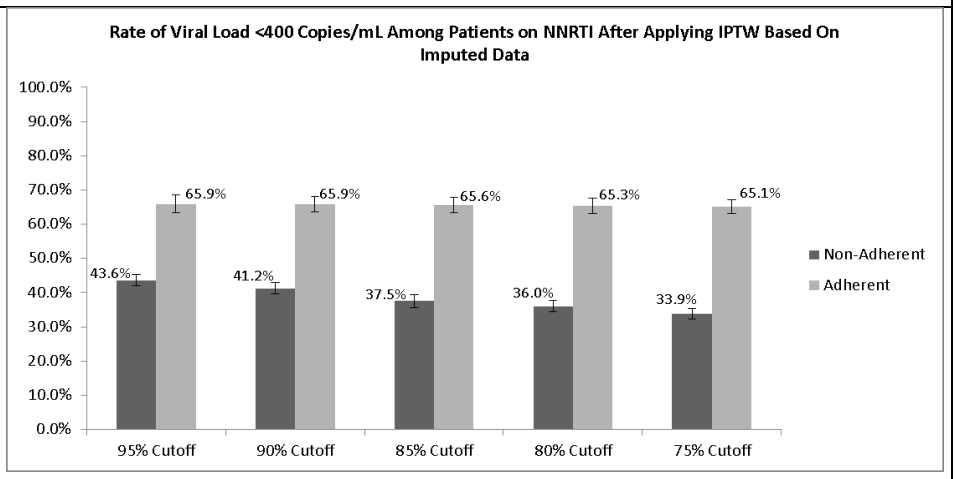
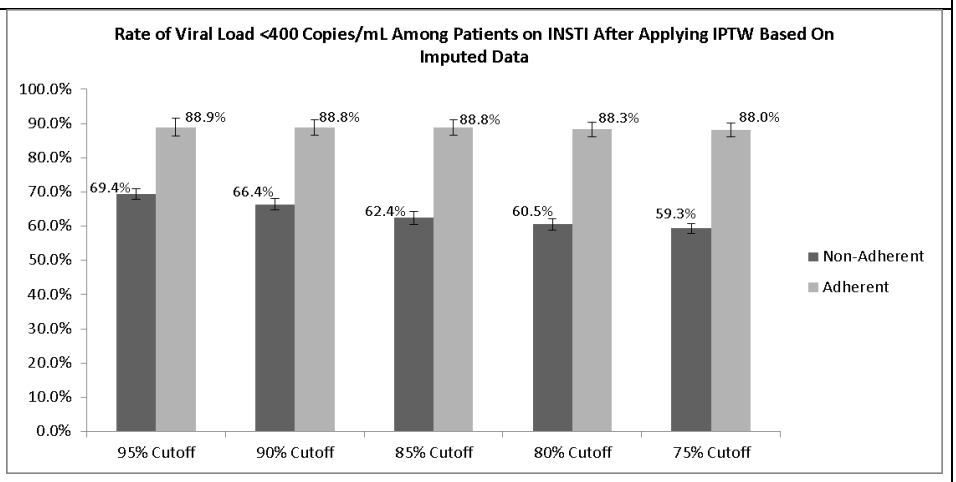
Regimen	Pooled Rate of Viral Load < 400 Copies/mL after Weighting IPTW Based on Five Imputed Datasets
NNRTI	
INSTI	

Figure A.5 Continued

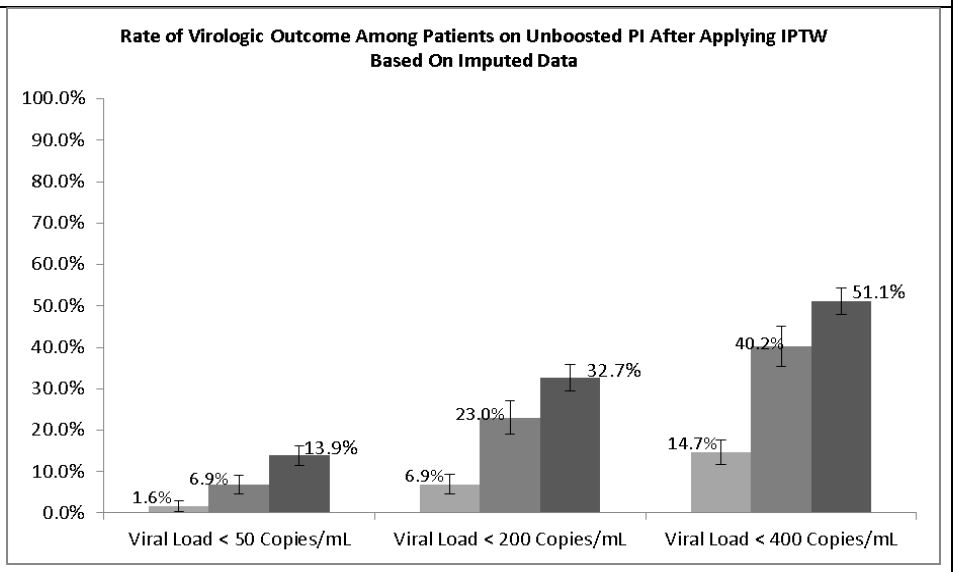
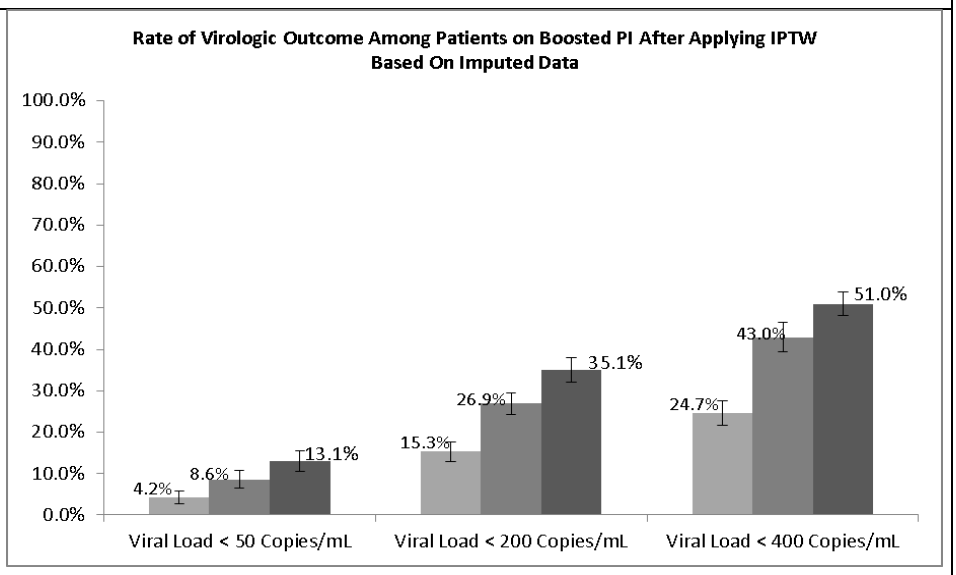
Regimen	Pooled Rate of Virologic Outcome by Multilevel Adherence after Weighting IPTW Based on Five Imputed Datasets
Unboosted PI	
Boosted PI	

Figure A.6 Rate of Virologic Outcome by Multilevel Adherence after Applying IPTW Based on Imputed Data

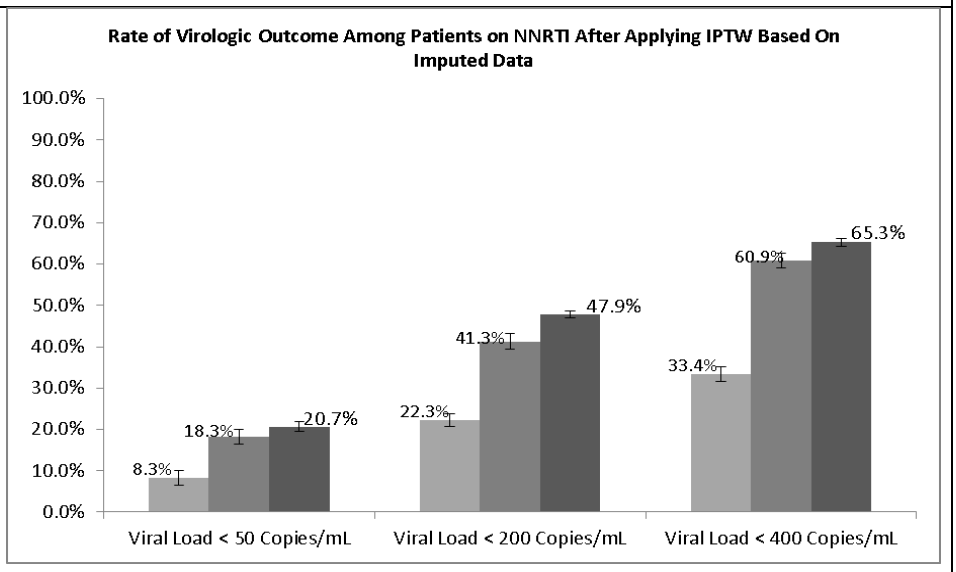
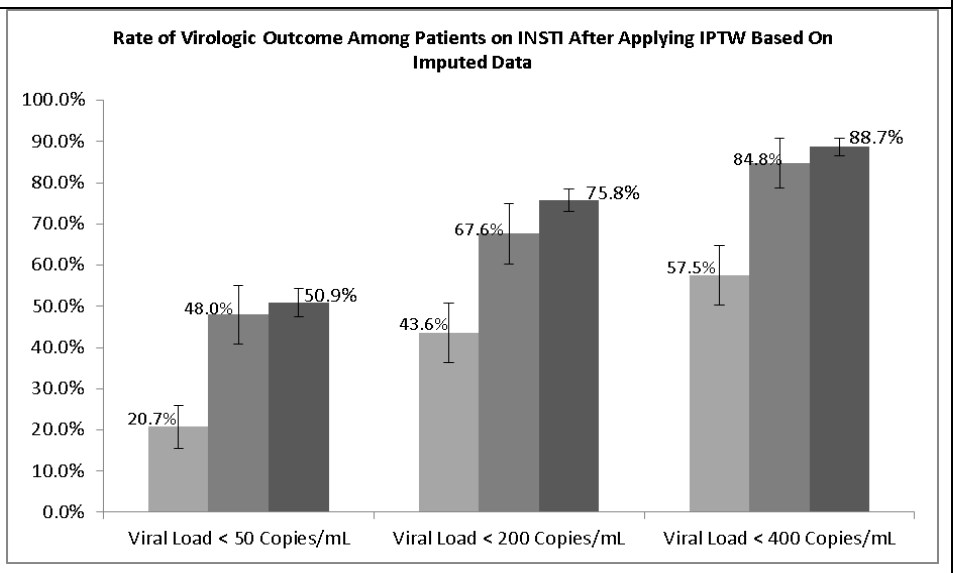
Regimen	Pooled Rate of Virologic Outcome by Multilevel Adherence after Weighting IPTW Based on Five Imputed Datasets
NNRTI	
INSTI	

Figure A.6 Continued

REFERENCE

1. What Is HIV/AIDS? 2014. at http://www.aids.gov/hiv-aids-basics/hiv-aids-101/what-is-hiv-aids/.)

2. HIV-2. 2014. at http://www.aidsmap.com/HIV-2/page/1322993/.)

3. A Call To Action - A Manual for Homeopaths in the Treatment of Patients with HIVAIDS. 2008. at http://www.homeopathycanada.com/call-action-manual-homeopaths-treatment-patients-hivaids-rebecca-gower-2008.)

4. CD4 cell counts. 2013. at http://www.aidsmap.com/CD4-cell-counts/page/1254931/.)

5. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2015. at http://aidsinfo.nih.gov/guidelines)

6. Viral load. 2014. at http://www.aids.gov/hiv-aids-basics/just-diagnosed-with-hiv-aids/understand-your-test-results/viral-load/.)

7. CD4 Count. 2014. at http://www.aids.gov/hiv-aids-basics/just-diagnosed-with-hiv-aids/understand-your-test-results/cd4-count/.)

8. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. 2014. (Accessed Oct 8, 2014, at http://www.who.int/hiv/pub/guidelines/keypopulations/en/.)

9. Guidelines version 7.0. (Accessed Oct 8, 2014, at http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf.)

10. Williams I, Churchill D, Anderson J, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013. All changed text is cast in yellow highlight.). HIV medicine 2014;15 Suppl 1:1-85.

11. HIV in the United States: At A Glance. 2014. at http://www.aids.gov/hiv-aids-basics/hiv-aids-101/statistics/.)

12. Estimated HIV incidence among adults and adolescents in the United States,

2007-2010. 2012. (Accessed Oct 8, 2014, at http://www.cdc.gov/hiv/library/slideSets/index.html.)

13. Life expectancy now considerably exceeds the average in some people with HIV in the US. 2014. (Accessed Oct 8, 2014, at http://www.aidsmap.com/Life-expectancy-now-considerably-exceeds-the-average-in-some-people-with-HIV-in-the-US/page/2816267/.)

14. Tengs TO, Lin TH. A meta-analysis of utility estimates for HIV/AIDS. Medical decision making : an international journal of the Society for Medical Decision Making 2002;22:475-81.

15. HIV Cost-effectiveness. 2014. (Accessed Oct 8, 2014, at http://www.cdc.gov/hiv/prevention/ongoing/costeffectiveness/.)

16. Pandhi D, Ailawadi P. Initiation of antiretroviral therapy. Indian journal of sexually transmitted diseases 2014;35:1-11.

17. Arnsten JH, Demas PA, Farzadegan H, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2001;33:1417-23.

18. Arnsten JH, Demas PA, Grant RW, et al. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. J Gen Intern Med 2002;17:377-81.

19. Aziz N, Sokoloff A, Kornak J, et al. Time to viral load suppression in antiretroviral-naive and -experienced HIV-infected pregnant women on highly active antiretroviral therapy: implications for pregnant women presenting late in gestation. BJOG : an international journal of obstetrics and gynaecology 2013;120:1534-47.

20. Bangsberg DR, Acosta EP, Gupta R, et al. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. AIDS 2006;20:223-31.

21. Braithwaite RS, Kozal MJ, Chang CC, et al. Adherence, virological and immunological outcomes for HIV-infected veterans starting combination antiretroviral therapies. AIDS 2007;21:1579-89.

22. Grossberg R, Zhang Y, Gross R. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. J Clin Epidemiol 2004;57:1107-10.

23. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. AIDS 1999;13:1099-107.

24. Julian FS, Martin P, Erickson SR. Validation of the Special Projects of National Significance adherence tool in HIV/AIDS patients. Annals of Pharmacotherapy 2010;44:1003-9.

25. Lima VD, Harrigan R, Murray M, et al. Differential impact of adherence on long-term treatment response among naive HIV-infected individuals. AIDS 2008;22:2371-80.

26. Maggiolo F, Airoldi M, Kleinloog HD, et al. Effect of Adherence to HAART on Virologic Outcome and on the Selection of Resistance-Conferring Mutations in NNRTI- or PI-Treated Patients. HIV Clinical Trials 2007;8:282-92.

27. Maggiolo F, Ravasio L, Ripamonti D, et al. Similar adherence rates favor different virologic outcomes for patients treated with nonnucleoside analogues or protease inhibitors. Clin Infect Dis 2005;40:158-63.

28. Marconi VC, Wu B, Hampton J, et al. Early warning indicators for first-line virologic failure independent of adherence measures in a South African urban clinic. AIDS Patient Care STDS 2013;27:657-68.

29. Messou E, Chaix ML, Gabillard D, et al. Association between medication possession ratio, virologic failure and drug resistance in HIV-1-infected adults on antiretroviral therapy in Cote d'Ivoire. J Acquir Immune Defic Syndr 2011;56:356-64.

30. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Annals of internal medicine 2000;133:21-30.

31. Wagner JH, Justice AC, Chesney M, Sinclair G, Weissman S, Rodriguez-Barradas M. Patient- and provider-reported adherence: toward a clinically useful approach to measuring antiretroviral adherence. J Clin Epidemiol 2001;54 Suppl 1:S91-8.

32. Gross R, Yip B, Lo Re V, 3rd, et al. A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 suppression. The Journal of infectious diseases 2006;194:1108-14.

33. Hong SY, Jerger L, Jonas A, et al. Medication possession ratio associated with short-term virologic response in individuals initiating antiretroviral therapy in Namibia. PloS one 2013;8:e56307.

34. Liu H, Miller LG, Hays RD, et al. Repeated measures longitudinal analyses of HIV virologic response as a function of percent adherence, dose timing, genotypic sensitivity, and other factors. J Acquir Immune Defic Syndr 2006;41:315-22.

35. Rosenblum M, Deeks SG, van der Laan M, Bangsberg DR. The risk of virologic failure decreases with duration of HIV suppression, at greater than 50% adherence to antiretroviral therapy. PLoS One 2009;4:e7196.

36. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2003;37:1112-8.

37. Parienti JJ, Barrail-Tran A, Duval X, et al. Adherence profiles and therapeutic responses of treatment-naive HIV-infected patients starting boosted atazanavir-based therapy in the ANRS 134-COPHAR 3 trial. Antimicrobial agents and chemotherapy 2013;57:2265-71.

38. Parienti JJ, Das-Douglas M, Massari V, et al. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. PloS one 2008;3:e2783.

39. Pasternak AO, de Bruin M, Jurriaans S, et al. Modest nonadherence to antiretroviral therapy promotes residual HIV-1 replication in the absence of virological rebound in plasma. J Infect Dis 2012;206:1443-52.

40. Shuter J, Sarlo JA, Kanmaz TJ, Rode RA, Zingman BS. HIV-infected patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of virologic suppression despite adherence rates less than 95%. J Acquir Immune Defic Syndr 2007;45:4-8.

41. Shuter J, Sarlo JA, Rode RA, Zingman BS. Occurrence of selective ritonavir nonadherence and dose-staggering in recipients of boosted HIV-1 protease inhibitor therapy. HIV Clin Trials 2009;10:135-42.

42. Sledjeski EM, Delahanty DL, Bogart LM. Incidence and impact of posttraumatic stress disorder and comorbid depression on adherence to HAART and CD4+ counts in people living with HIV. AIDS Patient Care STDS 2005;19:728-36.

43. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2006;43:939-41.

44. Bangsberg DR, Charlebois ED, Grant RM, et al. High levels of adherence do not prevent accumulation of HIV drug resistance mutations. AIDS 2003;17:1925-32.

45. Bastard M, Fall MB, Laniece I, et al. Revisiting long-term adherence to highly active antiretroviral therapy in Senegal using latent class analysis. J Acquir Immune Defic Syndr 2011;57:55-61.

46. Dragovic G, Salemovic D, Ranin J, Nikolic J, Kusic J, Jevtovic D. Clinical and immunologic outcomes of HAART-treated HIV-infected women in resource constrain settings: the Belgrade Study. Women & health 2014;54:35-47.

47. Ford N, Darder M, Spelman T, Maclean E, Mills E, Boulle A. Early adherence to

antiretroviral medication as a predictor of long-term HIV virological suppression: five-year follow up of an observational cohort. PloS one 2010;5:e10460.

48. Ghate M, Tripathy S, Gangakhedkar R, et al. Use of first line antiretroviral therapy from a free ART programme clinic in Pune, India - a preliminary report. The Indian journal of medical research 2013;137:942-9.

49. Huong DT, Bannister W, Phong PT, Kirk O, Peters L. Factors associated with HIV-1 virological failure in an outpatient clinic for HIV-infected people in Haiphong, Vietnam. Int J STD AIDS 2011;22:659-64.

50. Kerr T, Marshall BD, Milloy MJ, et al. Patterns of heroin and cocaine injection and plasma HIV-1 RNA suppression among a long-term cohort of injection drug users. Drug Alcohol Depend 2012;124:108-12.

51. Moreno A, Perez-Elias MJ, Casado JL, et al. Effectiveness and pitfalls of initial highly active antiretroviral therapy in HIV-infected patients in routine clinical practice. Antiviral therapy 2000;5:243-8.

52. Ncaca LN, Kranzer K, Orrell C. Treatment interruption and variation in tablet taking behaviour result in viral failure: a case-control study from Cape Town, South Africa. PloS one 2011;6:e23088.

53. Nellen JF, Nieuwkerk PT, Burger DM, Wibaut M, Gras LA, Prins JM. Which method of adherence measurement is most suitable for daily use to predict virological failure among immigrant and non-immigrant HIV-1 infected patients? AIDS Care 2009;21:842-50.

54. Parruti G, Manzoli L, Toro PM, et al. Long-term adherence to first-line highly active antiretroviral therapy in a hospital-based cohort: predictors and impact on virologic response and relapse. AIDS Patient Care STDS 2006;20:48-56.

55. Perez-Elias MJ, Moreno A, Moreno S, et al. Differences in durability of treatment with initial PI-based regimens. HIV Clin Trials 2003;4:391-9.

56. Perez-Elias MJ, Moreno A, Moreno S, et al. Higher virological effectiveness of NNRTI-based antiretroviral regimens containing nevirapine or efavirenz compared to a triple NRTI regimen as initial therapy in HIV-1-infected adults. HIV Clin Trials 2005;6:312-9.

57. Sha BE, Tierney C, Cohn SE, et al. Postpartum viral load rebound in HIV-1-infected women treated with highly active antiretroviral therapy: AIDS Clinical Trials Group Protocol A5150. HIV Clin Trials 2011;12:9-23.

58. Singh N, Berman SM, Swindells S, et al. Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 1999;29:824-30.

59. Sumari-de Boer IM, Sprangers MA, Prins JM, Nieuwkerk PT. HIV stigma and depressive symptoms are related to adherence and virological response to antiretroviral treatment among immigrant and indigenous HIV infected patients. AIDS Behav 2012;16:1681-9.

60. Carrieri MP, Raffi F, Lewden C, et al. Impact of early versus late adherence to highly active antiretroviral therapy on immuno-virological response: a 3-year follow-up study. Antivir Ther 2003;8:585-94.

61. Moore DM, Hogg RS, Yip B, Wood E, Harris M, Montaner JS. Regimen-dependent variations in adherence to therapy and virological suppression in patients initiating protease inhibitor-based highly active antiretroviral therapy. HIV medicine 2006;7:311-6.

62. Murri R, Guaraldi G, Lupoli P, et al. Rate and predictors of self-chosen drug discontinuations in highly active antiretroviral therapy-treated HIV-positive individuals. AIDS Patient Care STDS 2009;23:35-9.

63. Nieuwkerk PT, de Boer-van der Kolk IM, Prins JM, Locadia M, Sprangers MA. Self-reported adherence is more predictive of virological treatment response among patients with a lower tendency towards socially desirable responding. Antivir Ther 2010;15:913-6.

64. Pujades-Rodriguez M, Schramm B, Som L, et al. Immunovirological outcomes and resistance patterns at 4 years of antiretroviral therapy use in HIV-infected patients in Cambodia. Trop Med Int Health 2011;16:205-13.

65. Fairley CK, Permana A, Read TR. Long-term utility of measuring adherence by self-report compared with pharmacy record in a routine clinic setting. HIV medicine 2005;6:366-9.

66. Knobel H, Urbina O, Gonzalez A, et al. Impact of different patterns of nonadherence on the outcome of highly active antiretroviral therapy in patients with long-term follow-up. HIV medicine 2009;10:364-9.

67. Kuyper LM, Wood E, Montaner JS, Yip B, O'Connell J M, Hogg RS. Gender differences in HIV-1 RNA rebound attributed to incomplete antiretroviral adherence among HIV-Infected patients in a population-based cohort. J Acquir Immune Defic Syndr 2004;37:1470-6.

68. Le Moing V, Chene G, Carrieri MP, et al. Clinical, biologic, and behavioral predictors of early immunologic and virologic response in HIV-infected patients initiating protease inhibitors. J Acquir Immune Defic Syndr 2001;27:372-6.

69. Lopez JC, Moreno S, Jimenez-Onate F, Clotet B, Rubio R, Hernandez-Quero J. A cohort study of the food effect on virological failure and treatment discontinuation in patients on HAART containing didanosine enteric-coated capsules (FOODDIe Study).

HIV Clin Trials 2006;7:155-62.

70. Vallabhaneni S, Chandy S, Heylen E, Ekstrand M. Reasons for and correlates of antiretroviral treatment interruptions in a cohort of patients from public and private clinics in southern India. AIDS Care 2012;24:687-94.

71. Combescure C, Vallier N, Ledergerber B, et al. How reliable is an undetectable viral load? HIV medicine 2009;10:470-6.

72. Lima VD, Bangsberg DR, Harrigan PR, et al. Risk of viral failure declines with duration of suppression on highly active antiretroviral therapy irrespective of adherence level. J Acquir Immune Defic Syndr 2010;55:460-5.

73. Nachega JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, Maartens G. Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. Ann Intern Med 2007;146:564-73.

74. Wood E, Montaner JS, Yip B, et al. Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 infected injection drug users. CMAJ 2003;169:656-61.

75. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. The impact of adherence on CD4 cell count responses among HIV-infected patients. J Acquir Immune Defic Syndr 2004;35:261-8.

76. Van Vaerenbergh K, De Geest S, Derdelinckx I, et al. A combination of poor adherence and a low baseline susceptibility score is highly predictive for HAART failure. Antiviral chemistry & chemotherapy 2002;13:231-40.

77. Kobin AB, Sheth NU. Levels of adherence required for virologic suppression among newer antiretroviral medications. The Annals of pharmacotherapy 2011;45:372-9.

78. Cheng Y, Nebeker JR, Knippenberg KA, Nelson RE, Goetz MB, Lafleur J. Predicting Human Immunodeficiency Virus Veterans' Adherence to Antiretroviral agents via optimal data analysis. 2015 ISPOR; 2015.

79. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 2000;11:561-70.

80. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2013. at http://aidsinfo.nih.gov/guidelines)

81. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004;15:615-25.

82. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal

inference in epidemiology. Epidemiology 2000;11:550-60.

83. CDC. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. MMWR 2009;58:1-207.

84. CDC. Revised Surveillance Case Definitions for HIV Infection Among Adults, Adolescents, and Children Aged <18 Months and for HIV Infection and AIDS Among Children Aged 18 Months to <13 Years — United States, 2008. MMWR 2008;57:1-11.

85. Inter-Rater Agreement (Kappa). MEDCALC. at https://www.medcalc.org/manual/kappa.php.)

86. Bing EG, Burnam MA, Longshore D, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Arch Gen Psychiatry 2001;58:721-8.

87. Baillargeon JG, Paar DP, Wu H, et al. Psychiatric disorders, HIV infection and HIV/hepatitis co-infection in the correctional setting. AIDS Care 2008;20:124-9.

88. VA Research On Mental Health. (Accessed Oct 12, 2016, 2016, at http://www.research.va.gov/topics/mental_health.cfm.)

89. Shahoumian TA, Phillips BR, Backus LI. Cigarette Smoking, Reduction and Quit Attempts: Prevalence Among Veterans With Coronary Heart Disease. Prev Chronic Dis 2016;13:E41.

90. Cerrato E, Calcagno A, D'Ascenzo F, et al. Cardiovascular disease in HIV patients: from bench to bedside and backwards. Open Heart 2015;2:e000174.

91. Messiaen P, Wensing AM, Fun A, Nijhuis M, Brusselaers N, Vandekerckhove L. Clinical use of HIV integrase inhibitors: a systematic review and meta-analysis. PloS one 2013;8:e52562.

92. Ohl ME, Perencevich E, McInnes DK, et al. Antiretroviral adherence among rural compared to urban veterans with HIV infection in the United States. AIDS Behav 2013;17:174-80.

93. Horberg MA, Hurley LB, Silverberg MJ, Klein DB, Quesenberry CP, Mugavero MJ. Missed office visits and risk of mortality among HIV-infected subjects in a large healthcare system in the United States. AIDS Patient Care STDS 2013;27:442-9.

94. Fleishman JA, Gebo KA, Reilly ED, et al. Hospital and outpatient health services utilization among HIV-infected adults in care 2000-2002. Med Care 2005;43:III40-52.

95. Simoni JM, Huh D, Wilson IB, et al. Racial/Ethnic disparities in ART adherence in the United States: findings from the MACH14 study. J Acquir Immune Defic Syndr 2012;60:466-72.

96. DiMatteo MR, Haskard KB, Williams SL. Health beliefs, disease severity, and patient adherence: a meta-analysis. Med Care 2007;45:521-8.

97. Sax PE, Meyers JL, Mugavero M, Davis KL. Adherence to antiretroviral treatment and correlation with risk of hospitalization among commercially insured HIV patients in the United States. PloS one 2012;7:e31591.

98. Cole SR, Frangakis CE. The consistency statement in causal inference: a definition or an assumption? Epidemiology 2009;20:3-5.